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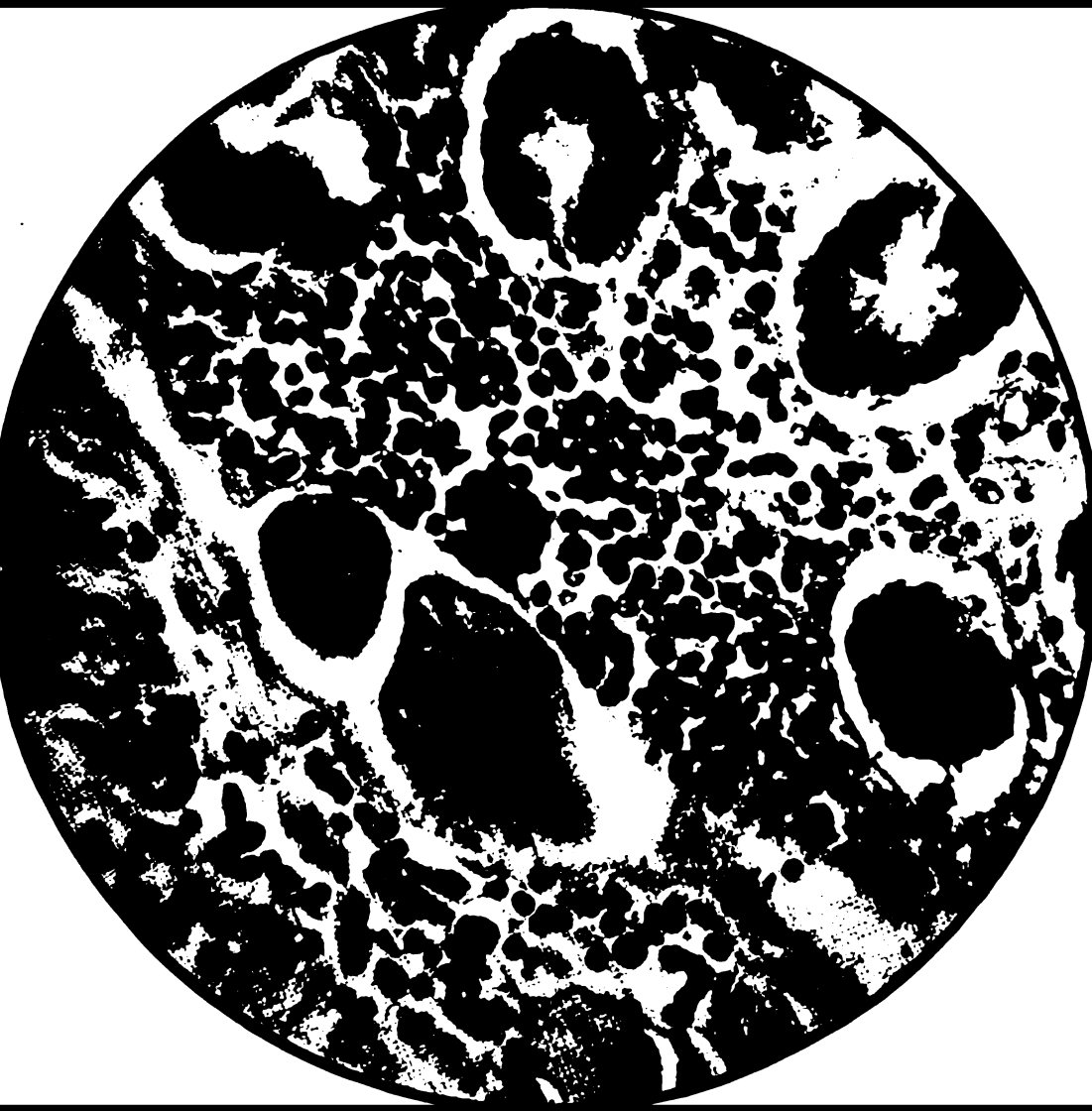

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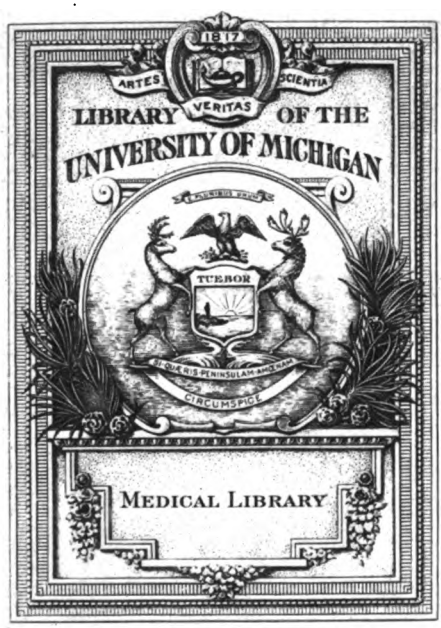

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TRANSACTIONS OF THE

SECTION ON

Pathology and Physiology

of the
American Medical Association
at the Sixty-Second Annual
Session, held at Los Angeles,
Cal., June 27 to 30, 1911

AMERICAN MEDICAL ASSOCIATION PRESS
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LIST OF OFFICERS

Those named below have served as officers in this section. This branch of the practice of medicine has been included with other subjects in the earlier years, as will be seen by the headings which denote the different section titles. The names of the officers have been taken from the published records, which are deficient in some cases. It will be appreciated if any additional data are brought to the attention of the Secretary of the American Medical Association.

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PROCEEDINGS OF THE SESSION

TUESDAY, JUNE 27—AFTERNOON

The meeting was called to order by the Chairman, Dr. Yandell Henderson, New Haven, Conn.

Drs. W. B. Cannon, Boston, and H. Gideon Wells, Chicago, were appointed a Committee on Nominations for officers for the coming year.

The Chairman stated that a number of applications for associate membership in the Association had been secured by officers of the Section. The Secretary read the names, and it was moved and carried that they be presented by the Delegate of the Section to the House of Delegates for election. [The House of Delegates elected them associate members.] The list was as follows:

Alsberg, Carl L., Bureau of Plant Industry. U. S. Department of Agriculture, Washington, D. C.

Beebe, S. P., Cornell University Medical College, Loomis Laboratory, 414 East 26th Street, New York.

Carrel, Alexis, Rockefeller Institute, 66th Street and Avenue A, New York.

Gies, William J., Department of Biologic Chemistry, Columbia University, New York.

Jackson, Dennis E., Washington University Medical School, 1906 Locust Street, St. Louis.

Maxwell, S. S., Department of Physiology, University of California, Berkeley, Cal.

Meigs, Edward B., Wistar Institute, Philadelphia.

Mendel, Lafayette B,. Professor of Physiologic Chemistry, Yale University, New Haven, Conn.

Murlin, J. R., First Avenue and 26th Street, Cornell University Medical School, New York.

Rockwood, E. W., Department of Chemistry, State University of Iowa, Iowa City.

Salant, William, Bureau of Chemistry, Washington, D. C.

Shaffer, Philip A., Washington University Medical School, 1806 Locust Street, St. Louis.

Sheldon, R. E., Anatomic Laboratory, University of Pittsburgh, Pittsburgh.

Simpson, Sutherland, Department of Physiology and Biochemistry, Cornell University Medical College, Ithaca, N. Y.

Snyder, Charles D., 1412 Bolton Street, Baltimore.

Stookey, L. B., Physiologic Laboratory, University of Southern California, Los Angeles.

Underhill, Frank Pell, Assistant Professor Physiologic Chemistry, Yale University, New Haven, Conn.

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Voegtlin, C., Department of Pharmacology, Johns Hopkins University, Washington and Monument Streets, Baltimore.

Pearce, Richard M., Department of Pathology, University of Pennsylvania, Philadelphia.

The Chairman, Dr. Yandell Henderson, read his address, entitled: "Clinical Physiology—An Opportunity and a Duty." Discussed by Drs. W. H. Cannon, Boston, and William H. Welch, Baltimore.

Drs. Cannon and Washman presented a paper on "The Nature of Hunger." No discussion.

A paper entitled: "The Relation of Specific Precipitation to the Reaction of Fixation," by Dr. Frederick R. Gay, Berkeley, Cal., was presented by Dr. G. Y. Rush, of the same place. Discussed by Dr. H. G. Wells, Chicago.

Dr. H. Gideon Wells, Chicago, read a paper on "Studies on Specificity." Discussed by Dr. Yandell Henderson, New Haven, Conn.

With the formal consent of the Section, Dr. W. T. Councilman, Boston, described a case of tuberculosis in an aneurysm. Discussed by Drs. W. H. Welch, Baltimore, and H. G. Wells, Chicago.

Dr. Jessie B. Hudson, Iowa, read a paper on "Bacteriology of the Ear." Discussed by Drs. W. H. Welch and Y. Henderson.

WEDNESDAY, JUNE 28—MORNING

Dr. Halden Jones, Los Angeles, read a paper on "Photogenic Bacteria." Discussed by Dr. Yandell Henderson, New Haven, Conn.

Dr. Leonard W. Ely, Denver, read a paper on "Observations on the Pathology of Joint Tuberculosis, with Lantern Slide Demonstration." No discussion.

Dr. J. F. Hultgen, Chicago, read a paper on "The Splenic Anemias." No discussion.

Dr. J. G. Van Zwaluwenburg, Ann Arbor, Mich., read a paper on "Heart Block." Discussed by Drs. A. W. Hewlett, Michigan, and Yandell Henderson, Connecticut.

Dr. W. D. Gatch, Baltimore, read a paper on "The Use of Rebreathing in the Administration of Anesthetics and as a Therapeutic Measure." Discussed by Dr. Yandell Henderson, Connecticut.

Dr. Gerald B. Webb, Colorado Springs, read a paper on "Immunity in Tuberculosis. Its Production in Monkeys and Children." Discussed by Drs. E. S. Bullock, New Mexico; J. F. Hultgen, Chicago; Roy E. Thomas, Arizona; E. R. Le Count, Chicago; M. P. Ravenel, Wisconsin; L. B. Wilson, Minnesota, and G. B. Webb.

Dr. E. R. Le Count, Chicago, read a paper on "Bone Hyperplasia and Tumor of Bone." No discussion.

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WEDNESDAY, JUNE 28—AFTERNOON

A paper on "The Pathogenesis of Balantidium Coli," by Dr. Fred B. Bowman, Manila, was presented by Dr. W. E. Musgrave, Manila. No discussion.

Dr. W. Ophuls, San Francisco, read a paper on "Subacute and Chronic Nephritis as Found in 1,000 Unselected Post-Mortem Examinations." Discussed by Drs. Leo Loeb, St. Louis, and W. Ophuls.

Dr. Samuel T. Darling, Ancon Hospital, read a paper on "Verruca Peruana." No discussion.

Dr. Glanville Y. Rusk, Berkley, Cal., read a paper on "Report of a Case of Diffuse Cerebral Sclerosis Occurring in Infancy." No discussion.

Drs. Howard T. Karsner and J. H. Austin, Philadelphia, presented a paper on "A Study of Experimental Bland Infarction." No discussion.

Dr. L. B. Stookey, Los Angeles, read a paper on "Some Urinary Findings in Eclampsia." Discussed by Dr. H. G. Wells, Chicago.

Dr. R. L. Thompson, St. Louis, read a paper on "The Influence of the Thyroid Gland on the Healing of Fractures." No discussion.

Dr. W. Warner Watkins, Phoenix, Ariz., read a paper on "The White Cells in Tuberculosis." Discussed by Drs. G. B. Webb, Colorado; Y. Henderson, Connecticut; J. T. Hultgen, Chicago, and F. M. Pottenger, California.

THURSDAY, JUNE 29—MORNING

The first order of business was the election of officers for the ensuing year. The Chairman called for the report of the Nominating Committee and the following officers were unanimously elected: Chairman, Dr. Leo Loeb, St. Louis; Vice-Chairman, Dr. William Ophuls, San Francisco; Secretary, Dr. A. W. Hewlett, Ann Arbor, Mich.; Delegate, Dr. E. R. Le Count, Chicago; Alternate, Dr. Yandell Henderson, New Haven, Conn.; Executive Committee, Drs. W. P. Rosenau, H. G. Wells and Yandell Henderson.

Dr. L. B. Wilson read from a paper on "Hypertrophy and Cancer of the Prostate," by Drs. L. B. Wilson and B. F. McGrath, Rochester, Minn. No discussion.

Other papers read were:

"The Pathogenesis of Interstitial Myocarditis and Hypertrophy of the Heart," by Drs. Leo Loeb and Moyer S. Fleisher, St. Louis. No discussion.

"The Relation of the Toxic Dose of Horse Serum to the Protective Dose of Atropin in Anaphylaxis," by Drs. Howard T. Karsner, and John B. Nutt, Philadelphia. No discussion.

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CLINICAL PHYSIOLOGY—AN OPPORTUNITY AND A DUTY

CHAIRMAN'S ADDRESS

YANDELL HENDERSON, PH.D.
Professor of Physiology, Yale Medical School
NEW HAVEN, CONN.

The time has come for the formal recognition of clinical physiology as a distinct subject and a field of work of the first importance. More or less inchoate, more or less dimly recognized, it already exists. The function which I wish to assume toward it to-day is rather that of a priest at the christening than that of a midwife at the birth of this latest-born and most neglected of the family of the medical sciences. I wish to give it the distinction of a name.

In the progress of medicine during the past decade, no feature has been more striking than the rapidity with which the advances in theoretic knowledge made in the laboratories of pathology and bacteriology have been adapted to the uses of clinical medicine. Physiology, on the contrary, has to a large extent led a life of mere self-development—like a proud virgin, beautiful, cold and sterile. I know that I risk the vigorous dissent of other physiologists in making this criticism. But I believe that it is needed not only for the good of medicine but for the best interests of physiology itself.

Science uncontaminated by any contact with the practical business of the world has in recent years been extolled in many an eloquent period. Priceless in their practical results have been the investigations made by great thinkers with no practical end in view. Nevertheless, I hold that none of the sciences, certainly none of

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the medical sciences, can long remain wholly divorced from contact with practical aims and yet continue fertile.

The appeal of clinical physiology is both to physiologists and to clinicians. Physiologists now and in the next few years will find their richest and most fruitful problems in the field of clinical, rather than in that of purely abstract, physiology. In the golden age of physiology our great predecessors, Claude Bernard, Brown-Séquard, Marey, Ludwig, Fritsch and Hitzig, and many others worked at topics which were at that time essentially problems of clinical physiology. Where in the literature of their day will you find anything to compare in ineptitude with the ponderous discussion of the mathematics of a membrane manometer, on which some of their successors in Germany now spend their time? Had not Voit's life work on nutrition a broadly utilitarian object? Was not Bernard working at the problem of diabetes when he discovered glycogen? And at animal heat with the problem of fever in mind, when he found the vasomotor nerves? We have dug enough ore from the depths for the present. Let us devote ourselves for a time to extracting some of the gold which it contains.

To clinicians in nearly all departments, physiology offers to-day a brilliant opportunity. The progress of medicine in overcoming the secrets of disease is like the siege of a walled city. The clinicians are the infantry. The laboratory workers are the sappers and miners, the heavy siege artillery and the aviation corps. It is useless to hurl infantry against an unbroken wall. When, however, a mine has been sprung or a bastion battered down, then is the time when good generalship will lead the infantry to the assault through the breach and over the fallen ramparts. The great breaches of the past few years, into which the infantry have stormed, have been those opened by pathology and bacteriology. Meanwhile physiology has not been idle. It has burrowed under

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and overthrown many of the strongest towers. What is needed now is the massed assault of the infantry. In simple words, there is in physiology to-day a great mass of knowledge and a wide range of methods readily adaptable to clinical uses and needs. If clinicians will acquaint themselves with this knowledge, and adopt, adapt and employ these methods, they will be able to march rapidly over obstacles now insurmountable.

Such a development of clinical physiology might well be the greatest event in the progress of medicine during the second decade of the twentieth century.

What the entire volume of clinical physiology should be in the future may most easily be shown by instancing such of its chapters as might be written even now. Such a chapter might be written about the clinical use of the sphygmomanometer, the significance of its measurements and the conceptions of circulatory functions which center in it. How valuable are these conceptions and measurements I need not emphasize before this audience! That which should be emphasized is the fact that physiologists began measuring blood-pressure in millimeters of mercury more than half a century ago; yet the clinical modification and utilization of the method is a matter of yesterday—perhaps I should rather say of to-day, or even to-morrow. Thus, by this example, it takes at least fifty years for a physiologic conception or method to find its way from the laboratory to the clinic. Many pathologic and bacteriologic methods complete the arduous journey in as many weeks.

It is only five years since I had the pleasure of attending a meeting of the British Medical Association at Toronto and of sitting in a great hall packed with clinicians, listening with open-mouthed interest to the wonderful news that the blood was under pressure in its vessels, that the pressure could easily be measured and that such measurements have a meaning. On this occasion a number of eminent authorities who had crossed

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the broad Atlantic, or traveled thousands of miles from the four quarters of Canada and the United States for this special purpose, thought it necessary to explain in words of one syllable how the heart pushes the blood through the arteries and how this pressure is measured by the raising of mercury in a tube of glass. Then arose one most eminent in authority who informed the audience in effect that using an instrument for such a purpose was all "bosh." For himself, he believed that the "tactus eruditus of the trained finger" told any competent physician or surgeon all that he needed to know!

I suppose that no one, however eminent, would dare make such an assertion to-day. We do not now have to explain what arterial pressure is. But turn for a moment from the clinical aspects of the circulation to those of respiration. Here is a function of the first importance; a function subject to manifold alterations in health and disease; easy to observe, relatively easy to measure; a function about which physiologists have locked in their laboratories a considerable amount of information. Yet look through all the hundreds of well-appointed hospitals between Los Angeles and Eastport in the state of Maine; look in all the elaborately equipped consulting rooms of all our eminent internists. Where will you find an instrument for anything more than the crudest observation and measurement of respiration? Nowhere, I believe! What do the clinicians of to-day—even the most learned—know of respiration? Next to nothing! And this little is mostly wrong.[1] If a patient pants for breath do not most of them order as many gallons of oxygen as his purse will allow to be blown off somewhere in the neighborhood? As well might they burn so many Chinese prayers printed on rice paper—except that it is profitable for the concern

1. So far as I am aware, the first paper ever written by an American clinician, based on a study of respiration in disease by precise physiologic methods, was presented as the oration in medicine at this meeting of the American Medical Association by Dr. C. F. Hoover.

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that supplies the oxygen. If, on the contrary, a patient's respiration is failing, oxygen may likewise be ordered; and a grim humor attaches to the fact that this oxygen, in order to comply with the requirements of the Pharmacopeia, has been carefully freed from every trace of carbon dioxid—the one substance which might act for a time to restore the respiratory center to its normal activity. Great is the medicine of to-day in its knowledge of man's parasites; great in its acquaintance with the appearance of his tissues after he is dead. But do we not lack an adequate comprehension of the functions of man himself, and a control of the working of the machine while, although somewhat damaged, it is still a "going concern?"

I am convinced that the now unutilized opportunities which modern physiology offers are so promising that any capable and well-trained physician or surgeon, if he will but take the trouble to acquaint himself with some one line of the subject—say respiration for example—and to work at it in connection with his practice, may make a notable contribution to practical medicine. What can be done in many lines may best be shown by instancing what has been done in a few. Consider the work of James Mackenzie, at first only a country doctor. With no better opportunities for work than a rural practice afforded he took the sphygmograph and applied it clinically. To-day his work on the application of graphic methods to the clinical study of diseases of the circulation stands as one of the finest chapters of clinical physiology.

The electrocardiogram is affording a similar opportunity for advancement in the clinical physiology of the heart, an opportunity which fortunately a number of internists in this country have seen and utilized. The new work of Hirschfelder of the Johns Hopkins School on diseases of the heart and aorta is throughout essentially a treatise in clinical physiology.

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On the side of surgery one of the most brilliant events of the past few years has been the development of methods allowing a ready access to the interior of the thorax. The work of Sauerbruch and Brauer, and of the other surgeons who have worked in this field, is a striking example of the profitableness of clinical physiology. So also is the work of Crile on surgical shock, and that of Cushing on the functions of the pituitary gland, normal and abnormal.

In a similar manner I might illustrate the sort of work which I believe that physiologists ought to do by examples of what some have done. Here may be mentioned the work of Erlanger on heart-block; of Cannon, not only on the normal movements of the stomach and intestines, but also on those after the performance of gastro-enterostomy, and of Meltzer in developing intratracheal insufflation from a method of mere laboratory interest into one which may prove of the greatest clinical utility.

All of these illustrations are drawn from the physical side of physiology. The physiologic chemists of to-day would easily afford ten times as many examples. In fact, the greater part of the flood of work which at present is almost swamping the journals of physiologic chemistry is essentially of this, to my mind, the right sort. It is directed to the solution, not of mere esoteric problems, but of topics of broad and pressing medical and human interest—diabetes, metabolism in disease as well as in health, and to those problems of nutrition which are of such tremendous import for the welfare of mankind.

It was a fortunate day for medicine when Emil Fischer turned his attention to the proteins. Almost at a stroke he lifted the pure and esoteric problems of biochemistry to a plane on which the great majority of chemical physiologists are incapable of working. Only a specially trained organic chemist can do this work. So our chemically-minded brethren, greatly to the profit of medicine and of their own scientific fortunes, have been forced to devote themselves to the cultivation of

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fields which will bear and are richly bearing fruit for to-day and to-morrow, rather than to that deeper ploughing and sowing from which the slow-growing harvest will indeed be of priceless value, but chiefly for generations yet unborn.

For the development of clinical physiology in America three conditions seem to be of special importance:

1. Internists and surgeons, and especially the professors of medicine and surgery in our medical schools, must be more interested, better trained and more widely read in physiology. It were better if they read less in the clinical and more in the scientific journals; better if they talked and practiced less, and investigated a great deal more.

2. Physiologists must assume the duty of teaching not only normal but also abnormal physiology. Both, in my opinion, should be taught in the second year of the medical course and as successive parts of one and the same subject. We cannot leave this for the pathologists to do. A man trained by autopsy and microscope is inevitably a morphologist. Just in proportion as he is fitted to deal with morphologic processes, he is unfitted to handle and expound functions of a physical nature—unless, of course, he happens to be an all-around genius.

3. Finally, I hold that in the future students who are being trained to be physiologists, whether in the field of physical and nervous or of chemical physiology, ought to have the M.D. degree. In our better medical schools the improvement of the curriculum in the last few years has been so marked that even the clinical courses have, to a great extent, lost that deadening influence on the students' ability to think scientifically which they formerly exerted. Furthermore, the elasticity introduced into the curriculum by the elective system, as practiced at Harvard and at Johns Hopkins, affords opportunities for the student who plans to be a physiologist to take little of what he will not need and to devote himself largely to his special interests.

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I do not regard the Ph.D. degree alone as insuring a sufficiently broad training for a physiologist, either in the chemical or physical line. It is true that many American physiologists are merely doctors of philosophy. I am such myself. But I know, by the sad experience of years wasted in filling in the gaps in an utterly insufficient technical training, how great a handicap this is. Any doctors of philosophy who profess a different view I am compelled to regard as like the fox in the fable who lost his tail. If they, like this cunning animal, claim that a condition of taillessness is an advantage, I would like to warn all the young physiologic foxes to beware. Grow a good bushy tail in the form of an M.D. after your name, and let no tailless old fox beguile you out of growing it.

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ABSTRACT OF DISCUSSION

Dr. W. B. Cannon, Boston: On the whole I am in hearty accord with the views expressed. It is true that there is in the Harvard Medical School a Division of Medical Sciences in which men are being prepared as teachers and workers in these sciences, and at the close of their training they are given —if they deserve it—a Ph.D. degree. That does not mean, however, that, so far as physiology is concerned, these men are unacquainted with its medical aspects. They are trained in the medical sciences—not only in physiology, but in physiologic chemistry, histology and pathology. It is true that they do not have the experience medical students get during the third year in the clinics, but I am inclined to think that the work of the third year clinics does not give an experience very serviceable for the defining of problems. The first clinical work is routine teaching of symptoms, an experience any man can get by a short period of observation. Acquaintance with such clinical teaching does not seem to me to give a man sufficient insight into clinical conditions to advance him much toward clinico-physiologic research. In physiologic research a man becomes interested in some particular field and naturally pays attention to all aspects of that field, including the clinical aspects. The fact that we have in this country at present men who have been trained as doctors of philosophy and who occupy chairs of physiology, and who are doing work in physiology which is important for medicine, indicates the possibilities of a man bringing out valuable knowledge because he allows his instincts to lead him to investigate beyond the limits of his routine training.

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THE BACTERIOLOGY OF THE EAR

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Determining the variety of bacteria present in disease of the ear is an aid to prognosis and warns us of possible complications. Single infections are usually acute, while mixed infections are apt to become chronic. There are very few cases of sinus thrombosis reported as due to pneumococci, but streptococcus sinus thrombosis is of common occurrence. Streptococci also frequently cause brain abscess and may involve important structures by necrosis, or may cause a fatal septicema. Hence, it is important to know whether these organisms are present. Streptococci and pneumococci appear to be the most frequent cause of otitis and mastoiditis. Staphylococci are found in a large percentage of chronic cases, seldom in pure culture.

Most investigators do not consider infection with staphylococci likely to be serious, but operation is necessary in about half the cases of infection with *Streptococcus pyogenes* or *Streptococcus mucosus*. If meningococci are found we know the patient has, or is likely to have, meningitis.

Examination of ear discharges is important in cases infected with diphtheria bacilli in order that proper precautions may be taken to prevent the spread of the disease. Newsholme (1904) reports a case of infection with diphtheria from a case of otorrhea—a pure culture of diphtheria bacilli being obtained from the ear discharge. Graham-Smith (1904) reports five cases, infected with virulent Klebs-Loeffler bacilli from contact with a patient having otorrhea. Several others have

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obtained virulent diphtheria germs from the ear. Diphtheria-like bacilli are often found in ear cases; a small percentage of these are virulent. Nuttall and Graham-Smith found 10 per cent. virulent. It is necessary to make cultural tests and animal inoculations before making a positive diagnosis of diphtheria.

In many reported cases, examination for bacteria was made only after puncture of the ear-drum. It is very difficult to sterilize the external auditory canal and drum-head so as to get uncontaminated cultures from the discharge. Leutert was the first to take cultures at the time of operation. He found streptococci predominating. In chronic cases staphylococci were most numerous. He thinks sinus thrombosis and brain abscess caused almost exclusively by streptococci. Newman and Rutten, in an article on "Etiology of Acute Otitis Media," come to practically the same conclusions. Libman found streptococci predominating. Barnhill and Wales report two-thirds of complications due to streptococci. McKenna says that *Streptococcus mucosus* is frequently found in otitis media, which explains its relative frequency as a cause of acute meningitis. Richardson mentions it as a cause of mastoid disease. Bacon thinks that most cases of acute otitis media are due to the influenza bacillus.

Infection may reach the middle ear through a ruptured drum-head, through the petrosquamosal fissure in the infant, through defects in the tegmen covered over with fibrous tissue, or in fracture of the temporal bone. It may travel along the nerve sheaths or blood-vessels, or the blood may carry infection to the ear. These cases, however, are rare. Microorganisms most frequently reach the ear from the nose and throat through the Eustachian tube. The chief predisposing factor is an inflammation of the nasopharynx or nasopharyngeal obstruction. Acute infection in the middle ear, with inefficient drainage or lack of proper treatment, is one of the most frequent causes of mastoiditis. A lowered

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vitality, exposure to wet and cold, and also certain constitutional diseases act as predisposing factors.

The question as to whether bacteria are present in the normal mastoid antrum is an important one. If they are present, then some relatively unimportant predisposing cause, as exposure to wet and cold, or loss of vitality from general or local causes, will give these bacteria an opportunity to develop and cause pathologic changes and loss of function, to a greater or less extent, and possibly serious complications.

Many investigators claim that the normal tympanic cavity and mastoid antrum contain pathogenic germs, few in number, which become active under favorable conditions. Others are just as positive that no pathogenic germs are present. The tympanum communicates with the Eustachian tube in front and with the mastoid antrum and cells behind. Since the Eustachian tube admits air to the middle ear, there seems to be no reason why it should not also admit bacteria from the throat.

A number of cases have been reported in which the mastoid was primarily involved. Two to 4 per cent. of typhoid patients have ear complications, the mastoid often being involved. Various organisms are found—staphylococci, streptococci, diplococci, colon bacilli, etc., thus apparently showing that a lowered vitality is the predisposing factor and that bacteria are already present.

In the following twenty-one cases, I have collected the material at the time of operation, made cultures and isolated and identified the bacteria. The material for examination was collected in sterile Petri dishes, and was then transferred to flasks containing 100 c.c. of sterile broth; an agar culture was also made by pouring agar on the material remaining in the Petri dish. These were incubated for twenty-four hours at 37 C, and then agar and gelatin plates were made. The plates were incubated from twenty-four to forty-eight hours. The colonies were then examined—methylene-

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blue and Gram stains being made, also hanging drops to determine motility, after which cultures were made from the different colonies on the various sugar media, on gelatin, blood-serum, milk, litmus milk, potato, and glucose and lactose bouillon. Where necessary, smears were stained for spores, capsules and flagella.

REPORT OF CASES

Following are given the synopses of twenty-one cases as taken from the history sheets:

CASE 1.—N. G., aged 19. September 29, complains of a discharge from the left ear, a roaring sound in the ear, and constant headache. Trouble started four years ago and has gradually become worse. Complains of a slight sore throat. At first, ear discharged only when lying on left side. No pain at that time. Complains of pain only when she catches cold in ear. Discharge night and day. Cannot hear very well with left ear. Whooping-cough when 2 years old and measles at 12. Perfectly well at present except for ear trouble. In left ear bone, conduction is better than air.

Diagnosis.—Chronic discharge from left ear, chronic mastoiditis left.

Operation.—October 1, radical mastoid—left.

Bacteriology.—Staphylococci and an unknown bacillus in left tympanic cavity. Streptococci found in left ear, December 6.

November 19, double suturing of left mastoid wound. Discharged February 9.

October 5, ear began discharging last Thursday and has been discharging ever since. March 8, left ear has been discharging for last two weeks. Sense of fulness in left side of head. Dull ache back of left ear.

Result.—Complete recovery. No improvement in hearing in left ear.

CASE 2.—E. T., aged 13. November 3, complains of earache in left ear. Ear has discharged for many years. Some impairment of hearing. Aches only in winter. Trouble starts as soon as cold weather sets in. Discharge and ear-ache whenever patient catches cold. Past history not known, patient being an adopted child.

Examination.—Bone and air conduction equal in left. Drum-head badly scarred.

Diagnosis.—Adenoids and diseased tonsils, chronic otorrhea—left.

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Operation.—November 5, left radical mastoid with dura exposed.

Bacteriology.—Streptococci, *Staphylococcus aureus* and *albus.*

Plastic Operation.—November 19.

An autogenous vaccine was prepared and given every seven days in the following doses:

FIRST—	
Streptococci	5,000,000
Staph. alb.	100,000,000
Staph. aureus	100,000,000
SECOND—	
Streptococci	10,000,000
Staph. alb.	200,000,000
Staph. aureus	200,000,000
THIRD—	
Streptococci	15,000,000
Staph. alb.	400,000,000
Staph. aureus	400,000,000
FOURTH—	
Streptococci	20,000,000
Staph. alb.	600,000,000
Staph. aureus	600,000,000
FIFTH—	
Strept.	30,000,000
Staph. alb.	80,000,000
Staph. aureus	800,000,000
SIXTH—Same as Fifth.	

Result.—Complete recovery; patient gained in weight, and health much improved.

CASE 3.—H., schoolboy.

Diagnosis.—July 17, serous catarrh middle ear.

Operation.—Simple mastoid—left.

Bacteriology.—Staphylococci.

Operation.—August 4, adenoids and tonsils removed.

Result.—Complete recovery.

CASE 4.—R. B., aged 2.

Diagnosis.—February 23, acute mastoiditis, both sides.

Operation.—February 25, right simple mastoid.

Bacteriology.—Streptococci. March 6, diphtheria bacilli found in culture from right ear. The diphtheria bacilli were tested and found to be virulent.

Operations.—March 8, left simple mastoid. Sutured right. April 1, sutured left mastoid.

Discharged May 14.

CASE 5.—S. C., aged 22. April 24, complains of a growth on right mastoid. Commenced eight years ago. At times, patient says, it seems to puff up and then go down again.

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There has been no pain and no discharge. Never dizzy that she can remember. At times the growth is somewhat painful when pressure is made.

Diagnosis.—Mastoiditis.

Operation.—April 24, simple mastoid.

Pathology.—Enlarged glands over mastoid region, tip of mastoid somewhat diseased. Antrum normal. Laboratory report: One of the glands was sectioned and found to be lymphoid tissue, somewhat inflamed. Culture from the antrum showed numerous bacteria, including *Staphylococcus albus.*

Result.—Complete recovery.

CASE 6.—N. N., complains of loss of hearing and discharging ear. About two years ago noticed hearing was affected. The discharge began about six months ago.

Operation.—May 20, radical mastoid—right.

Pathology.—Dura exposed over tympanic cavity. Extensive necrosis along posterior wall.

Bacteriology.—Gram-negative streptococci, *Staphylococcus albus.*

Operation.—June 4, sutured right mastoid.

Result.—Complete recovery, hearing normal.

CASE 7.—F. A., aged 8. September 29. Ear trouble began two years ago. Had scarlet fever with diphtheria following. Had tonsils removed when he had diphtheria. Left ear began to discharge then and has been discharging nearly all the time since. Some better the past year. Had ear-ache at times before discharge began. Had to cleanse ear three or four times a day. Odor offensive. Mastoid region painful once in a while. Right ear discharged for a short time after attack. Hearing bad in left ear.

Examination.—Right ear normal. Left ear, high notes normal. Bone conduction better than air. Whisper, one foot; speaking voice, four feet. Perforation of drum-head, discharge from ear.

Diagnosis.—Chronic otorrhea.

Operation.—September 3, radical mastoid.

Pathology.—Necrotic bone removed from middle fossa exposing dura. Attic filled with granulations. Removed hammer. Found many cells about external auditory canal. Necrotic material next dura and pachymeningitis. Surface of dura inflamed, dura not bulging.

Bacteriology.—*Sarcina aurantiaca* and rhodococcus.

Result.—Complete recovery, no improvement in hearing in left ear.

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CASE 8.—L. D., aged 17. October. Trouble began in right ear about a year ago, caused by a bad cold. Had severe pain in ear and mastoid tenderness for about a week. Could not hear well with that ear. There was a discharge for a few days at first. Has not discharged since then but has had much pain in ear and back of ear. For the last month pain has been constantly present.

Examination.—Right ear, high notes normal. Air conduction better than bone. Small hemorrhages on lower half of drum-head. Whisper, 15 feet; speaking voice, 40 feet. Caloric test showed labyrinth functionating. Left ear normal.

Operation.—October 7, simple mastoid—right.

Pathology.—Necrosis below antrum and over angle of lateral sinus. All cells inflamed.

Bacteriology.—Sarcina was the only organism found. Patient completely recovered.

CASE 9.—Patient, aged 26. October 29 had had trouble with right ear for thirteen years, since scarlet fever. For the last three months it has been discharging constantly—pain at times.

Examination.—Perforation in drum-head. Right tube open. Ear might get well with packing and inflation. Right ear, whisper 4 inches; speaking voice 20 inches. Left ear, whisper 15 feet; speaking voice, 35 feet.

November 28. Needs radical mastoid.

Operation.—December 1, right radical mastoid.

Pathology.—Exposed lateral sinus at knee; sinus was thickened and covered with granulations. Necrosis down to facial canal; necrosis above and posteriorly. Polyps in tympanic cavity. Facial nerve unaffected after operation.

Bacteriology.—*Staphylococcus aureus.*

Result.—Complete recovery from operation; no improvement in hearing.

CASE 10.—G. R., aged 10. November 9. Complains of ear trouble. Had tonsillitis four weeks ago, and after a few days his left ear began to discharge. Had ear-ache in left ear during his attack of tonsillitis and just before the ear began to discharge. The discharge stopped last Saturday, when he noticed a swelling behind his ear. Says it is not sore unless he presses it. Hearing somewhat impaired. Does not breathe through his nose at night and only a part of the time during the day. Had measles when 8 years old. Past medical history otherwise negative.

Diagnosis.—Acute mastoiditis.

Operation.—November 11, left simple mastoid. Adenoids removed.

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Pathology.—Open sinus leading into antrum. Much pus present. Dura not exposed. Parasinus abscess and external dural abscess. Lateral sinus exposed full length.

Result.—Complete recovery.

Bacteriology.—Streptococci.

CASE 11.—H. J., aged 16. November 18. Hurt in a runaway in March. Unconscious three or four hours. Has had trouble back of ear and in back of head since. Both ears discharged some at times since then. Has had paracentesis of left ear-drum once, and of right, three or four times. This relieves pain for a time. Pain begins in back of head and head throbs. Tenderness over right mastoid extending back almost to occipital protuberance since accident. Had vomiting spell just after accident but none since. Headache all the time.

Examination.—Right and left ears normal.

Diagnosis.—Traumatic mastoiditis or periostitis and osteitis.

Operation.—November 2, right simple mastoid. Removal of necrotic bone posterior to mastoid region, exposing lateral sinus and dura.

Pathology.—Circular area of necrotic bone below lateral sinus three and one-half inches posterior to external auditory canal. Extended to dura. Periosteum black over this area. Periosteum peels off with difficulty. Mastoid antrum and cells normal. Posterior emissary vein one inch posterior to mastoid. Lateral sinus exposed. Dura exposed in right occipital region and appears normal.

Bacteriology.—*Staphylococcus albus* and *aureus* and an unknown bacillus found in mastoid antrum.

December 17, ear began to pain and drum was bulging. Paracentesis done. Found only serum. *Staphylococcus albus* found in discharge. January 12, Paracentesis right drum. February 16, discharged—perfectly well.

CASE 12.—R. F., schoolboy. November 1. Says his ears have discharged ever since he can remember. No other history obtainable.

Examination.—Right ear, yellowish discharge. Perforated drum-head. High notes normal. Bone conduction better than air. Whisper 3 feet; speaking voice 10 feet. Tests show labyrinth functionating. Left ear—yellowish discharge. Perforated drum-head. High notes normal. Bone conduction better than air. Whisper, 15 feet; speaking voice, 30 feet. Tests show labyrinth functionating.

Diagnosis.—Double chronic otorrhea.

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Operations.—November 4, right antromeatal. Adenoids removed. November 11, left radical mastoid. November 18, plastic operation.

Pathology.—All mastoid cells necrotic. Lateral sinus not exposed. Pus in attic. Exposed dura. Pachymeningitis.

Bacteriology.—Pneumobacillus.

Pathology.—Tip necrotic. Necrosis anterior and external to facial—very extensive. Much necrosis at opening of Eustachian tube. One arm of incus gone. Malleus in fair shape. Cerebellum exposed just under lateral sinus.

Bacteriology.—Pneumobacillus.

January 2, left ear well; right improving. No improvement in hearing in left; about two-thirds normal in right.

CASE 13.—L. C., aged 17. November 26. Left ear discharged when a baby. No discharge after that for six or seven years. Since then, whenever he catches cold the ear discharges. Discharge yellowish, has bad odor. No pain in ear. No pain or swelling over mastoid region. Thinks he cannot hear with this ear.

Examination.—Right ear, air conduction better than bone. High notes cut down. Whisper, 15 feet; speaking voice, 40 feet. Left ear, high notes cut down. Bone conduction better than air. Whisper, 6 inches; speaking voice, 25 feet. Tests showed labyrinth functioning. Perforation of drum the size of pea.

Diagnosis.—Chronic otorrhea.

Operation.—December 2, left radical mastoid.

Pathology.—Complete necrosis of mastoid. Posterior fossa exposed. Exposed dura. Shiny material in antrum.

Bacteriology.—*Staphylococcus aureus* and *Micrococcus tetragenus.*

Patient developed slight facial paralysis December 4, which lasted until December 13. Went home before ear was well. Not known whether he had further trouble.

CASE 14.—W. W., aged 17. November 5. Had tonsils removed ten years ago. Two years ago adenoids removed. Since that operation, ears have been discharging almost constantly. Turbinates large and fibrous. Remains of tonsils infected. Left, voice, 8 inches; right, whisper, 10 feet. Advised to have nose repaired first, and at same time have ear treated twice a day. Later, if necessary, mastoid operation.

October 7, acute tonsillitis. October 19, left inferior turbinate trimmed. Has a very high arch with an overhanging bite. Arch should be widened. November 16, right inferior turbinate trimmed. November 26, paracentesis left drum-head.

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Operation.—December 19, left meatomastoid. Dura exposed in middle fossa; lateral sinus exposed and whole mastoid necrotic.

Bacteriology.—Colon bacillus and *Bacillus diphtheriæ.*

Result.—Patient well, no further trouble with ear, hearing about one-fourth of normal.

CASE 15.—E. G., aged 16, December 13, complains of discharging ears. Puffing noise constantly in right ear. Says hearing is impaired in right ear. Normal in left. When a baby, had discharge from both ears; does not remember how long it lasted. Seven years ago one discharged, does not remember which one or how long it lasted. Last April he had mumps on both sides and two weeks later measles. Ears both began to discharge when the patient had mumps. Left one discharged for two months, right one ever since—occasionally stopping for a day or two at a time. Some pain below right ear and in front of mastoid. No pain or swelling behind ear. Discharge was of a yellowish color, profuse and had an offensive odor. Has been treated for past three months.

Physical Examination.—Pus in external meatus. Drum-head thickened. High notes normal Air conduction better than bone. Whisper, 2 feet; speaking voice, 12 feet. Test showed labyrinth functionating. Adenoids present. Punctured right and left nasal antrum and found a small amount of old pus in left.

Diagnosis.—Mastoiditis, right.

Operation.—December 16, right simple mastoid, also adenoids removed.

Pathology.—Eburnated bone in cortex. Antrum and neighboring cells filled with pus.

Bacteriology—Pneumobacillus.

December 30, taken to isolation ward for erysipelas beginning about 1 inch anterior to right ear. Began December 28. January 2, had a little tenderness over tip of left mastoid. January 3, swelling on left side of neck just below mastoid.

Operation.—January 12, paracentesis—right. Discharged. March 1, comes back because her right ear is discharging—started two weeks ago. Discharged April 7. Ears well, hearing about one-half normal in right ear.

CASE 16.—A. P., aged 16. December 15. Was slow in learning to talk. At times hears fairly well. When he takes cold, hearing is affected. To-day hears loud voice at 6 inches only. Sleeps with mouth open.

Examination.—Left drum-head scarred and retracted. Right external canal filled with pus. Right ear, loud voice, 6 inches; left ear, cannot hear speaking voice. Tonsils and adenoids should be removed. Needs a meatomastoid operation.

Operation.—December 16, radical mastoid.

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Bacteriology.—Colon bacillus.

Operation.—December 28, adenoids removed.

Result.—Complete recovery from operation; hearing in right ear about one-half normal.

CASE 17.—E. V., aged 15, January 7. Ear trouble began one week ago last Monday. Left ear began to ache, continued to ache for a couple of days, and then began to discharge. Has been discharging ever since and is painful most of the time. Mastoid region swollen after ear began to discharge. Had influenza and sore throat about one week before ear trouble began. Says she had ear-ache a great deal about eight years ago; does not remember which ear or whether it discharged any. Breathes through mouth day and night. When she catches cold has a dull pain over right antrum. Had ulcerated tooth on right side above one or two years ago. Nose constantly discharges—yellowish—no odor.

Physical Examination.—Right ear normal. Left ear, perforation of drum-head with discharge of pus. Drum-head bulging. Tenderness over mastoid. Pain in ear most of the time. High notes normal. Bone conduction better than air.

Diagnosis.—Left otorrhea and mastoiditis.

Operations.—January 7, paracentesis left ear-drum. January 13, left simple mastoid.

Pathology.—Mastoid cells small and all filled with pus. Not much necrosis. Exposed lateral sinus at knee.

Bacteriology.—Streptococci, some of them Gram-negative. *Micrococcus catarrhalis.* Hay bacillus.

Discharged February 15. Ears normal.

CASE 18.—M. G., aged 16. January 16. Has had trouble in right ear as long as she can remember. If she catches cold, she has ear-ache. Three or four years ago had ear-ache in right ear a great deal. One year ago, right ear discharged for two or three weeks. Discharge was purulent. Since then no discharge until middle of December, when she had measles. December 26, had a severe ear-ache; discharge began and has continued ever since, stopping at times for a day or two. Ear has been very painful; was swollen over mastoid region a part of the time. Ear and mastoid region have been massaged by an osteopath. Says she had tonsillitis several years ago, also on left side, when she had measles. Has had sore throat occasionally and could open her mouth only one-half inch.

Physical Examination.—Tenderness over mastoid. Pulsating ear-drum. Abscess under temporal muscle. High notes normal. Bone conduction better than air conduction.

Diagnosis.—Mastoiditis—right. Probably abscess under temporal muscle.

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Operation.—January 20, right simple mastoid. Paracentesis right ear-drum.

Pathology.—Abscess in temporal muscle. Pus in mastoid antrum. Exposed lateral sinus. Badly necrosed bone extending to dura. Has pachymeningitis and perisinus abscess, with inflammation of walls of sinus. Dead bone lying next to brain and attached to dura. Bone between temporosphenoidal lobe and sinus all rotten. Granulations on lateral sinus. No evidence of leptomeningitis or local brain abscess. Dura not tense.

Bacteriology.—Staphylococci and Gram-negative streptococci.

February 10, sutured right mastoid. February 26, patient came back for examination; was to come twice a week for treatment. April 4, discharged—ear well.

May 11. Has come back for treatment of other ear. Hearing improved.

CASE 19.—L. R., aged 19. January 26. Right ear began aching January 25. Discharge began January 26; purulent and bloody. Soreness over mastoid; left ear aching some at present.

Operation.—February 23, simple mastoid, right. Results good.

Pathology.—All mastoid cells necrotic; dura not exposed.

Bacteriology.—*Streptococcus* and *Staphylococcus albus.*

Results.—May 13. Discharged, complete recovery.

CASE 20.—Mrs. L., aged 41. February 1. Sunday morning had an ear-ache. Right ear pains; has roaring in ears; hears water running, katydids, etc.

Examination.—Left drum-head retracted; pain on pressure over tip of right mastoid. Right ear, loud voice 4 feet; left, whisper 3 feet.

Diagnosis.—Right ear, abscess with mastoid involvement. Had ulcerated upper molar on right side. Just above second molar on right side is a discharging sinus. Has had discharge from nose before. Exploratory puncture of right antrum; lots of pus.

Diagnosis.—Empyema of antrum of Highmore secondary to necrotic tooth.

Operation.—February 3, right simple mastoid. Infected with gas-producing organism; gas bubbled up when antrum was approached and also when ear-drum was cut. Pain in antrum.

Bacteriology.—*Streptococci, Micrococcus aerogenes capsulatus* and *B. subtilis.*

Operation.—Right radical antrum, middle and third molars removed. With the third there came away a part of the

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alveolar process, which was necrotic, and left an opening into the antrum. Antrum was filled with polyps.

March 24, canal has been dry for several days.

May 2, mastoid and antrum well. Return for closure of opening between antrum and mouth. Result normal.

CASE 21.—M. G. March 3. Last Wednesday had a sore throat and right ear started to ache, is still aching. Has a sense of fullness in right side of head. Mastoid region very tender. Glands at angle of jaw very painful. Six weeks previously had appendicitis and was operated on. A few days later temperature rose to 105 F., and examination showed an abscess at site of operation. Bacteriologic examination of the pus showed streptococci. She recovered from this and was about to be discharged from the hospital when the ear trouble began.

Ear discharged when she was a very small child. Also discharged last year. Tonsils become inflamed whenever she catches cold. Are inflamed now. Cannot see very well; wears glasses. Has headache, photophobia; eyes water a great deal.

Left ear normal. Right ear, drum head bulging and a little red. Slight tenderness at mastoid tip. Bone conduction better than air conduction. High notes normal; whisper, 10 inches; speaking voice, 6 feet.

Operations.—March 3, paracentesis, right ear. March 10, right simple mastoid.

Pathology.—Necrosis of antrum; dura over middle fossa and lateral sinus exposed. Granulations over middle fossa on dura.

Bacteriology.—Gram-negative streptococci.

This case is particularly interesting from the fact that the ear infection followed so soon after the appendicular abscess and was caused by the same organism. The infection was evidently carried by the blood. Recovery complete.

In two of these cases the mastoid antrum was normal and pathogenic bacteria were found. In one other case not included in this series, I found pathogenic bacteria in the normal antrum.

There were thirteen chronic cases and six acute cases. In seven chronic cases, staphylococci were found. In only two cases were they the only organism found. In three of the chronic cases streptococci were present, but not in pure culture. In two chronic cases pneumobacilli were found in pure culture. Colon bacilli were

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found in two chronic cases, once in pure culture, once with *Bacillus diphtheriæ.*

Diphtheria bacilli occurred as a secondary infection in one acute case. In the six acute cases streptococci were found, three times in pure culture. In one acute case Gram-negative streptococci were the only germs found. Staphylococci were found in one acute case—not in pure culture. *Micrococcus aerogenes capsulatus, Micrococcus catarrhalis* and *B. subtilis* were found in mixed infections. In many cases no history was obtainable as to the cause of the disease. In two cases ear trouble followed scarlet fever; in one mumps and measles; in one influenza; in one tonsillitis; in one removal of adenoids; in one the disease followed empyema of the antrum of Highmore, secondary to a necrotic tooth. One was made worse by an attack of measles. Five cases were aggravated by taking cold. In most of the chronic cases and in one acute case, necrosis was extensive. It did not appear to be worse where streptococci were present.

SUMMARY AND CONCLUSIONS

1. Bacteria are normally present in the mastoid antrum. This is to be expected since there is a continuous passage from the throat through the Eustachian tube and middle ear to the antrum.

2. Mastoiditis is caused by a variety of organisms. Those found in my cases were *Staphylococcus, Streptococcus, Micrococcus catarrhalis,* diphtheria bacillus, *B. coli communis,* pneumobacillus, *B. aerogenes capsulatus, Micrococcus tetragenus,* sarcina, and *B. subtilis.*

3. In three cases of ear disease Gram-negative streptococci were found.

4. The few patients who were treated with vaccines after operation were remarkedly benefited.

I wish to thank Dr. Dean for the opportunity of studying these cases, also for the suggestions he has given me in my work, and for the use of his private library.

207 North Capitol Street.

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BANTI'S SYMPTOM-COMPLEX

WITH REPORT OF A CASE

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CHICAGO

Patient.—A. H., aged 35, druggist, was admitted to the Englewood Hospital, Nov. 3, 1910. He is a patient of Dr. Charles Piper, through whose kindness I am allowed to study this case.

History.—Sick, or sickly, a good deal; always delicate and pale, but without history of any definite disease until eight years ago, when he contracted syphilis, for which he was treated as well as his rather free habits would permit. Three years ago he consulted Dr. Belfield, who observed the splenomegaly, and advised further energetic antiluetic therapy. The patient used tobacco moderately, and alcohol to excess at intervals; denied any drug addiction.

Examination.—Patient was a thin, icteroid, emaciated, sickly-looking man, with large abdomen, very pale visible mucous membranes and without fever. With all these objective symptoms, he seemed rather optimistic. He complained of great weakness, but no pain, vomiting, nausea, or headache. Appetite was poor; patient had diarrhea for last two or three days before admission; no hemorrhage at any time. Fingers and tongue were tremulous; speech showed some stuttering. Tongue moist, slightly furred; gums pale, yet intact. Pupillary reflexes were negative; patellars exaggerated. Quinquaud's sign present. The lungs, joints, glands and throat were negative. The heart showed a small bruit over the apex; systolic, short, not transmitted to the left; no cardiac hypertrophy, no arrhythmia. Pulse 84, of rather low tension; no basal pulmonary congestion; no edema of the legs. The abdomen was prominent, walls thin; skin smooth, but not discolored. There was a distinct bulging of the left hypochondrium, and moderate prominence of the right upper abdomen. Movable dulness; succussion thrill and ballottement of upper abdominal organs left no doubt as to the presence of a large amount of free fluid in the belly cavity. The spleen was very large, hard, moderately movable and slightly tender; its free border felt distinctly notchy. It extended to a full hand's breadth below

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the left costal border. The upper splenic border was at its normal level, and the organ showed no sign of ptosis. The liver was distinctly enlarged; its edge was rather dull and a trifle irregular; it was not tender to ordinary pressure. There was no special tenderness over the gall-bladder.

The urine showed no bile, no albumin, no sugar; distinct reaction for urobilin.

The blood: reds, 2,100,000; distinct poikilocytosis; no polychromatophilia, no nucleated reds. Hemoglobin, 45 per cent. (Tallquist). Whites: 2,600. Differential: polynuclears 77.8 per cent., small mononuclears 15.7 per cent., large mononuclears 4.5 per cent., eosinophils 2 per cent.

Course.—The patient gradually gained in appetite, strength and appearance. His weight began to improve slowly, hand in hand with the recession of the ascites and the diminution in size of the spleen and liver. Moderate subicterus remained. His progress may be traced graphically in Chart 1. The treatment consisted in mixed mercury and iodid of potassium medication. In April three successive doses of sodium cacodylate were given by intramuscular injection, but this arsenic therapy was abandoned because of the marked intolerance to it. Mr. A. H. had been able to attend to light professional duties and his condition on May 18, 1911, showed the following symptoms: "Subicteric, yet pale, rather thin; tremulous lips and fingers. Eats and sleeps fairly well, but tires easily and lacks ambition. No headache, no eye or ear troubles; no hemorrhages, and no pains. Ascites greatly diminished, liver and spleen just palpable. Urine shows urobilin, no bile, no albumin, no sugar; microscopically negative. Wassermann reaction (Dr. Mefford) positive.

"Blood: reds, 3,600,000; moderate poikilocytosis, no nucleated reds, no polychromatophilia; hemoglobin 90 per cent. (Tallquist). Whites, 5,300. Differential: polynuclears 57.6 per cent., small mononuclears 37.7 per cent., large mononuclears 3.8 per cent., eosinophils 0.9 per cent. No abnormal cells."

Patient was planning how he could earn more money, and a few days later he entered on a new occupation, which required considerable physical and mental exertion. After a week, his condition had aggravated again; a rather severe gastro-enteritis (*Brechdurchfall*) occurred, a slight exacerbation of the icterus without acholic stools, and fever, rather rapid pulse and severe headache. The blood-curves show the deterioration of his hematopoietic system. A few nucleated red blood-cells appeared and the poikilocytosis increased (see Chart 1). Three weeks afterward he was again improving.

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INTERPRETATION OF THE ANAMNESTIC, CLINICAL AND HEMATOLOGIC FINDINGS IN THIS CASE

A man who always had been frail and sickly, without any history of purpura or of hemorrhage, contracted syphilis eight years ago and was treated for it in the usual way. His splenomegaly was recognized two years ago (Dr. Belfield). There is no history of any antecedent marked icterus. The patient's habits readily

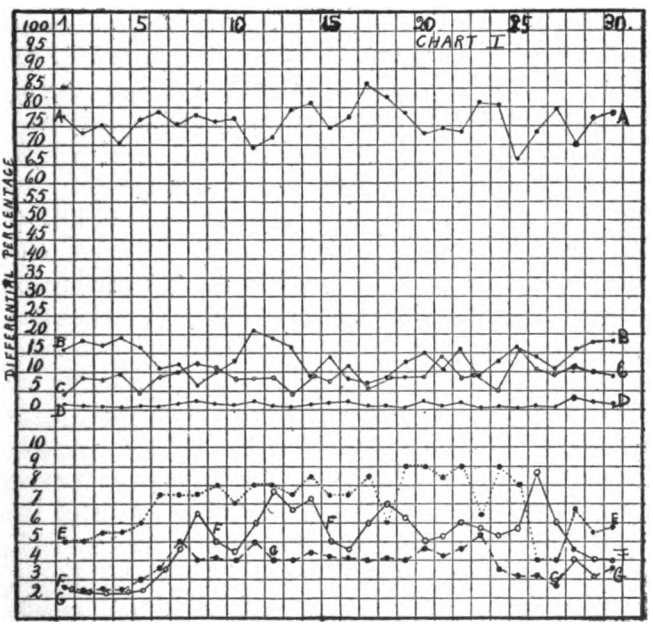

Fig. 1.—Chart showing blood-picture of splenic anemia. Thirty consecutive counts in one case. A indicates polynuclears; B, small mononuclears; C, large mononuclears; D, eosinophils; E, hemoglobin; F, total whites; G, total reds. The column to the left indicates differential percentages. Note (1) the constant parallelism between the curves of hemoglobin, white blood-cells and red blood-cells; (2) the very frequent synchronous movements, and (3) the uniformity of each curve in both charts.

suggested alcoholic cirrhosis as a primary diagnosis, and a cursory physical examination seemed to confirm it. Repeated, careful blood-counts, however, led to further examinations, and to the recognition of a symptom-

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complex characteristic of splenic anemia.[1] A brief review of the clinical, pathologic and hematologic data of such cases shows at once the scarcity of diagnostic criteria.[2] Yet on serious reflection it seems to me that the splenomegaly is the central figure in the clinical picture of these anemias, and that the name of Banti's symptom-complex fits the disease better, and emphasizes better Banti's splenogenic[3] theory than any other. By this I mean to accept in their widest meaning Dock and Warthin's,[4] and Warthin's[5] finding of phlebosclerosis, and calcareous degeneration of the splenic and portal veins, which they explain as following a primary thrombosis of these blood-vessels. Theirs is the merit to have called attention to the rôle of splenic and portal phlebosclerosis as an etiologic factor in this symptom-complex, but they fail to suggest an antecedent endophlebitis as the initial lesion in this vicious circle. This seems to me more probably the case, since in the first ten days of typhoid fevers there is an almost identical blood-picture with splenomegaly, and some oligocythemia. The early generalized endothelia-cell hyperplasia, according to Mallory one of the characteristics of typhoid fever pathology, accounts for the frequent phlebothromboses occurring in these affections. The toxin-laden venous blood irritates the endothelial cells of the walls of the veins, and thus conduces to thrombosis, venous stasis, passive hyperemia, irritation of the reticulum, or stroma, or both, with subsequent disturbance of the splenic functions. The question as to whether in splenic anemia the plastic or the lytic functions of the spleen[6] are individually or jointly involved cannot be settled as yet,

1. Hunter, W. K.: Infantile Splenic Anemia, Lancet, Jan. 23, 1909, p. 226.
2. Aschenheim, E.: Toxic Hemolytic Icterus with Splenomegaly, Folia hematologia, Berlin, Feb. 28, 1911, xi.
3. Grawitz: In Schwalbe's Lehrbuch der Greisen Krankheiten, Berlin, 1909, p. 144.
4. Dock and Warthin: Am. Jour. Med. Sc., 1904, cxxvii, 24.
5. Warthin, A. S.: Relation of Thrombophlebitis of the Portal and Splenic Veins to Splenic Anemia and Banti's Disease, Internat. Clin., 1910, iv, 188.
6. Arneth, J.: Diagnose und Therapie der Anemien, Würzburg, 1905, p. 113.

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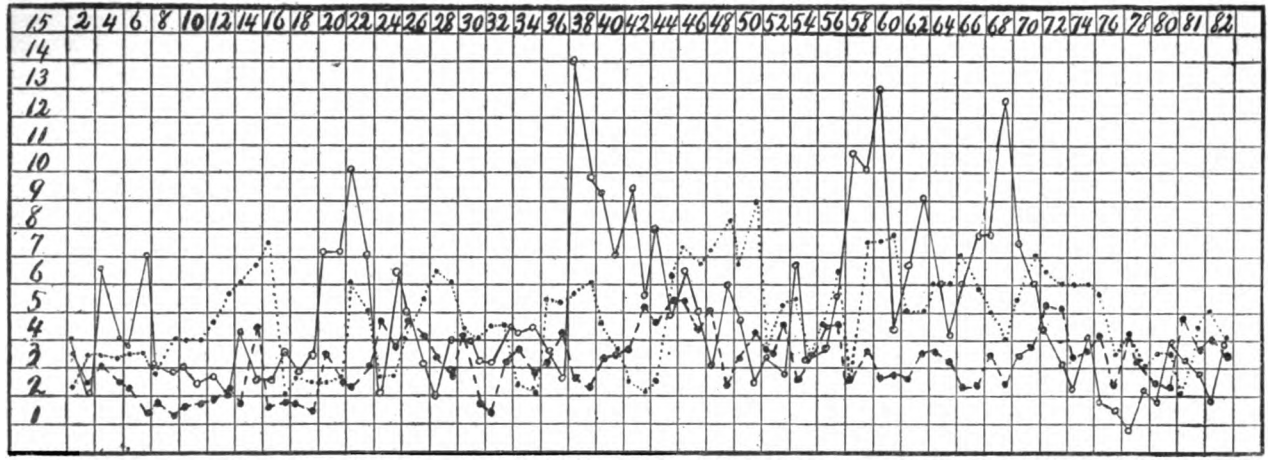

Fig. 2.—Chart showing eighty-two hemoglobin, total red and white counts determined from the literature. **Line of small and large solid dots** indicates hemoglobin; in **percentage units broken line with** solid dots, total red blood-cells, in **million units; solid line with hollow dots, total white blood-cells, in thousand units. Notice that the** blood-picture of Banti's symptom-complex **remains pathologic throughout, in one or more of its ingredients.**

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but the study of the foregoing shows that the curves of the red blood-corpuscles, of the hemoglobin, and of the total leukocytes show distinctly parallel and mostly synchronous movements. This, I can interpret, not as signs of hematolysis, but of a slow or bradyplastic hematopoiesis, as a disturbance of the entire blood-forming system. The splenomegaly is due to an active irritative inflammation of Malpighian bodies and of the stroma. Bradyhematopoiesis is, in my opinion, the underlying hematologic basis of the Banti symptom-complex. It is sluggish production of blood, due to antecedent impoverishment of the blood-forming tissues, especially of the spleen, that we have to deal with here, not an anhematopoiesis as Auburtin[7] thinks. Splenic anemia is not an objectionable term, Naegeli's[8] and others' opinion notwithstanding; it designates a symptom-complex which is more closely akin to pernicious anemia[9] than to leukemia.

The fact that splenic endophlebitis in my case is of luetic nature, as in that of Willy Schmidt's,[10] or of kala-azar spirochetic origin, as in Marchand's case,[11] should in no way prevent us from considering the splenomegalic anemia as a clinical entity, just as a nephritis retains its identity no matter what its etiology may have been. It is hardly probable that splenic anemia may be a dormant leukemia.[12] On the contrary, I believe it to be the last stage of an extinct leukemia, hence its lack of permanent recuperability, and its striking rarity in children. My charts show that at no time during the course of splenic anemia does the blood become normal in all of its ingredients; either the

7. Auburtin, Charles: Les anémies par anhématopoèse, Semaine méd., March, 1910, p. 337.
8. Naegeli, O.: Diagnostik des Blutes und der Blut-Krankheiten, 1908, p. 395.
9. Hill, R. A. P.: Splenic Anemia and Hemochromatosis, St. Barth. Hosp. Rep., London, 1909, liv, 43.
10. Schmidt, Willy: Banti's Diseases with Heredo-Syphilis, München. med. Wchnschr., March 21, 1911, No. 12.
11. Masuda, Niro: A Case of Banti's Disease, etc., Med. Klin., Jan. 15, 1911, p. 104.
12. Hirschfeld, H.: Banti's Disease, Deutsch. Klin., 1909, p. 324.

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erythrocytes, leukocytes or the hemoglobin are subnormal, singly or together (see charts). Reasoning *a priori*. Banti's disease must be rare in childhood, on account of the resiliency of the hematopoietic system in children. In fact, Weil and Clerc never saw a case of this in a child.[13] The same hematopathic cause would produce in a child an anemia infantum pseudoleukemica of von Jaksch. If, then, the Banti symptom occurs so rarely or not at all in childhood, it is well to add that a von Jaksch anemia in a child is the equivalent of a splenic anemia in the adult for reasons detailed above. It must, however, be kept in mind that a strict clinical or hematologic separation from another of primary blood-diseases is often impossible. Their relation is often close and plainly evident, as can be seen from the following short classification of the generalized primary affections of the hematopoietic system. These I have divided according to their essential hematology, and subdivided according to their etiology and clinical course.

CLASSIFICATION

1. Polycythemias: With splenomegaly.
   Without splenomegaly.
   a. Idiopathic, primary (Vaquez).
   b. Secondary.
2. Anemias.
   a. Idiopathic, primary, essential (Addison).
      Plastic.
      Hyperplastic.
      Aplastic.
   b. Secondary, pernicious, progressive (Biermer).
      Plastic.
      Hyperplastic.
      Aplastic.
3. Ictero-anemias.
   a. Acquired, hemolytic (Widal).
   b. Congenital (Minkowski-Chauffard).
   c. Congenital,[14] family-type (Gaucher).

13. Weil and Clerc, in Hutinel's Maladies des Enfants, Paris, 1909, p. 411.
14. Brill, Mandelbaum and Libman: Primary Splenomegaly of the Gaucher Type, Am. Jour. Med. Sc., 1909, cxxxvii, 84.

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4. Splenic anemias (Griesinger).
   a. Primary, splenomegalic or Banti's disease.
   b. Secondary, splenomegalic, kala-azar malarial, syphilitic, etc.
   c. Leukanemia (v. Leube), combining the features of pernicious anemia and leukemia, alternately or conjointly.
5. Pseudoleukemias (Cohnheim) or aleukemias.
   a. Anemia infantile, pseudoleukemic (v. Jaksch).
   b. Lymphatic, idiopathic, pseudoleukemia or Hodgkin's disease.
   c. Secondary, tuberculous, lymphatic pseudo-leukemia or Sternberg's disease.
6. Leukemias (Virchow).
   a. Lymphocytic: Small.
      Large, or Rieder form.
   b. Myelocytic.
   c. Polynuclear.
   d. Mixed.
   e. Chloroma: Lymphocytic.
      Myelocytic.

The above classification of primary blood-diseases is intended to give a general comprehensive view of the generic relationship between all of them. It will also show the central position of splenic anemias, between those primary blood-affections involving the erythrocytes exclusively, mainly or partially, and those involving the leukopoietic tissues, such as the leukemias and pseudoleukemia. It is evident that the spleen plays an active rôle here[15] and not a neutral one. In point of frequency, Banti's disease holds a middle place as can be learned from my statistics, from cases seen in consultation or in my private practice from October, 1904, to June 20, 1911. Of thirty-nine cases of primary hematopathic diseases, there were thirteen of pernicious anemia, eight of splenic anemia, eight of leukemia, six of infantile pseudoleukemic anemia (von Jaksch), two cases of acquired hemolytic icterus, one case of Sternberg "peculiar" lymphatic tubercular pseudoleukemia, and one case of leukanemia. About 20 per cent., or eight out of

15. Lewis, M. J.: Splenic Anemia, Splenectomy, Recovery, etc., Am. Jour. Med. Sc., August, 1908, p. 157.

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thirty-nine primary blood-affections in my practice were of the Banti symptom-complex.

Its course is of intermittent character, as first observed by Strumpell.[16]

The diagnosis rests on the presence of the splenomegaly, the anemia with leukopenia, and the ascites. Any case with hematologic findings leaning repeatedly toward leukemia should not be included under splenic anemia. The prognosis as to life in Banti's symptom-complex is fair when the blood-picture occupies and retains its central position, but becomes rapidly bad in the proportion as it recedes from its center to one or the other extreme.

The therapy of splenic anemia, to judge from my case, should be conservative, although Sutherland and Burghard, as well as Banti,[17] were in favor of splenectomy. The undoubtedly generic nature of this symptom-complex calls for further study of the mechanism of the various hematopathic findings. The parallelism and synchronicity of the erythrocytic, leukocytic and hemoglobin curves, the absolute fatality of the disease, the intermittent and very chronic course of the affection argue not for an infectious process, but for a cause organic and anatomic in nature, and of unknown origin.

5037 South Ashland Avenue.

16. Mossler: Pseudoleukemia Splenica, in Ziemssen's Handbuch der speziellen Pathologie und Therapie, 1878, viii, 110.
17. Sutherland and Burghard: Treatment of Splenic Anemia by Splenectomy, Proc. Roy. Soc. of Medicine, January, 1911, iv, 58.

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THE PATHOLOGY OF JOINT TUBERCULOSIS

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It may seem somewhat bold for an orthopedic surgeon to address the members of an august body like this on a matter pertaining to their own specialty, and were there anything like a unanimity among you, I should hesitate.

That the greatest confusion exists as to the pathology of joint tuberculosis, one can easily find by consulting a few text-books and by reading a few articles on the subject. This confusion, of course, is reflected in all the aspects of the disease, and until the exact pathology is laid down in full and comprehensive terms, it is futile to look for any scientific treatment of the disease. In other words, although the cause of the disease has been known for many years, the failure of the pathologist to place the pathology on a sound footing, is responsible for the chaos in the whole subject of joint tuberculosis.

In self-defense, then, I entered on this work, to see what I could find out for myself, and I shall here attempt to set forth as briefly as possible some of my findings. My material consists of about eighty specimens, supplied by various men. Most of the specimens consist of resected joints, some of amputated extremities, and a few of clippings from joints that had been opened for one purpose or another.

The first question to be discussed is, where joint tuberculosis starts and what tissues it affects. It starts in the marrow of the spongy bone ends or in the cellular synovia, and as long as it remains uncomplicated, it is confined to one of these two tissues or to them both.

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The bone itself, the cartilage and the ligament are damaged simply by interference with their nutrition, and may be said to play a purely passive part in the disease. The tendency in recent years in America has been to regard all joint tuberculosis as of bony origin, and the theory has the attraction of simplicity, but, starting out myself with this view, I have been compelled to abandon it.

A study of our specimens and of the histories of the patients from whom they were taken convinces me that primary synovial disease not only occurs but is quite frequent in adults. In children, disease of the bone-marrow predominates. The reason for this we shall presently see. Synovial tissue is distinctly vulnerable to tuberculosis. It is classed among structures of the lymphatic system. We find the disease rather frequently in tendon sheaths.

The next point is, why tuberculosis occurs in the extremities of the long bones and not in the shafts. As you know, various explanations have been advanced for this phenomenon, but as you also know, none of them has ever been accepted as adequate. Liability to injury has been said to be responsible, but trauma is no cause of tuberculosis, and if we injured a muscle or a ligament, or if we fractured a bone, we should not expect tuberculosis to ensue, and we must not forget that the tissues of a joint are adapted generally to the traumata to which they are exposed. Some say that the vulnerability is due to the arrangement of the blood-vessels, to the lack of anastomosis in the end arteries of the epiphyses in childhood, but the anastomosis is present in adults, and the lack of anastomosis in the blood-vessels of the brain, for instance, does not predispose to cerebral tuberculosis. To congestion has been ascribed a causal rôle, but congestion has been advanced as a means of curing the disease.

About a year ago, I proposed an explanation which appeared to me quite adequate, and I see no reason as

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yet to change my opinion. Bone tuberculosis is simply a question of red or lymphoid marrow. Wherever in bone we find lymphoid marrow, there we find the bone vulnerable to tuberculosis, and where we do not find it, there we do not find unmixed tuberculosis. This might be regarded as a coincidence, but the argument is reinforced by the fact that after a resection of a joint, the knee for instance, if bony union and primary healing be attained, the structure of the bone at that site changes from spongy to dense, and the disease disappears, whether or not we have removed all the infected tissue. There is no difference between dense and spongy bone except the arrangement of the lamellæ, the amount of bone, and the quality of the marrow, and we have already seen that the bone itself is never affected.

In the spongy bone we find the red or cellular, or lymphoid marrow, and where we find lymphoid tissue there tuberculosis can get a foothold. There is more red marrow in the bones of children than in those of adults. Hence, bone tuberculosis is more frequent in the former than in the latter. Primary tuberculosis of the shafts of the long bones has been described, but almost always, or invariably, of the shafts of children's bones alone, and red marrow exists in them. Joint tuberculosis is rare in children under 1 year of age. Their bone ends are composed almost exclusively of cartilage, and Rovsing has said that the joint tuberculosis of infants was probably always purely synovial. The yellow marrow appears to be invulnerable, but if a secondary infection be added then the disease may spread here also, as well as to other tissues also previously immune.

When we find a tissue subject to tuberculosis in a certain region and find further that when this tissue disappears, the disease dies out, we are certainly justified in regarding these facts as having some sort of a causal relation to the disease.

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König has attached great importance to the precipitation of fibrin from the exudate in the joint. By means of this fibrin he has asserted that the cartilage is eroded and destroyed from the joint side, and that the synovia is infected from the exudate. In fact, he seems to assign to the exudate a very important part in the spread of the disease. I am forced to the conclusion that his examination of joints must have been almost exclusively macroscopic. I assign to the exudate a minor rôle and regard it more or less as a mere symptom, and quite unimportant in the pathology. I think the synovia is invaded by the primary tubercle in its substance, or else by a spread of the disease from the bone, where the synovia is attached at the margin of the cartilage.

The "layers of fibrin" which König describes on the cartilage, I think, are simply the evidence of the fibrillation of the superficial layers of the cartilage, caused by the interference with its nutrition and by the immobilization of the joint. The fibrillation can be plainly seen in sections. The cartilage may be perfectly smooth in joints which have been for years the seat of a tuberculous exudate. I have the joints to prove this. On the other hand, the fibrillation (or "layers of fibrin") may not be in evidence in a cartilage that has been lifted off the subjacent bone. If this bone is in good condition, that is, if the nutrition of the cartilage has not been involved, the cartilage will usually be found in pretty good condition. I believe that it is never damaged except from below.

The subject of rice bodies has also attracted some attention. Two theories have been held in regard to them: that they were the result of the precipitation of fibrin, or of a degenerative process. I consider them as the product of an effective attempt at repair, as the walling off of the tuberculous granulations and subsequent condensation and shrinking. One of our specimens (a knee-joint) contained a collection of them in a fibrous capsule. I think that the slide of this specimen

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is unique. The joint also contained a small encapsulated hematoma. Both are rare—one may be the later stage of the other.

PYOGENIC MEMBRANES

In almost all text-books tuberculous abscesses and sinuses are described as being lined by a pyogenic membrane; that is, by a wall of granulation tissue, filled with tubercles. The walls of these abscesses or sinuses, *if they are not infected secondarily with pus germs,* are composed of the necrotic tissue of the structures in which they lie. If the tissue is vulnerable to pure tuberculosis, then tubercles may be found in the walls of the abscesses or sinuses, otherwise they will not be found there. In a cross-section of the walls of a secondarily infected tuberculous sinus, tubercles will be seen, in one not secondarily infected they will not be seen. The importance of this fact to the subject of treatment is at once obvious.

What is the result of an old healed tuberculosis of a joint or of a tuberculosis thought to be healed? One hears the term "ankylosis" used somewhat at random, and more or less vaguely. In children, one may occasionally get a bony ankylosis, but only after a secondary infection. In not one of our specimens of adult tuberculous joints was a bony ankylosis present. I believe that it never occurs except after a resection.

As to healing, what may one expect? In a child, anything from good function and a practically complete cure, up to a bony ankylosis. In an adult, I believe that if the bone be involved, painless and useful function in that joint is at an end forever, and permanent healing under conservative treatment is very doubtful. In one of our resected adult knees, we found an old healed tubercle in the bone, just beneath the cartilage, buttressed off with fibrous tissue and bony trabeculæ, and yet, the disease must have broken out afresh or the joint would not have been excised. In another case, an

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ankle, we found an old tubercle buried in fibrous adhesions. In some of our cases, the history runs back for years.

Finally, let me mention the unreliability of the examination of a clipping from a joint for diagnosis. Tuberculosis may exist in one part of the synovia and not in another. The reports of different laboratories from sections of the one joint will often differ. If tuberculous tissue be found, the report, of course, is final; if not, the joint may still be tuberculous.

Thorough mastery of the pathology of joint tuberculosis by the profession would soon put an end to the diverse, and sometimes fantastic, treatment of the disease, which now prevails.

440 Humboldt Street.

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IMMUNITY IN TUBERCULOSIS

ITS PRODUCTION IN MONKEYS AND CHILDREN *

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AND
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In former publications[1, 2] we have shown that large numbers of virulent tubercle bacilli may be inoculated into guinea-pigs without producing tuberculosis, provided that very few bacilli are at first inoculated, and that the numbers are increased slowly. In addition, Lieb[3] has shown the possibility of inoculating rabbits with virulent bovine tubercle bacilli in a similar manner.

The work now reported will indicate that monkeys (*Macacus rhesus*), animals which, when kept in captivity are exceedingly vulnerable to tubercle bacilli, can also be safely given increasing amounts of virulent human tubercle bacilli, if inoculated in a manner similar to that in which the animals above referred to were inoculated.

Twelve monkeys (*Macacus rhesus*) were procured and were tested with Old Tuberculin according to Römer's[4] method for cattle. A positive reaction is indicated by at least a 75 per cent. increase in the measurement of the skin-fold.

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* From the Laboratory of Cragmor Sanatorium.

1. Webb, Williams and Barber: Immunity Production, etc., Jour. Med. Research, xx, No. 1; Immunity Production, etc., Tr. VI Internat. Cong. of Tuberc.
2. Webb and Williams: Immunity in Tuberculosis, Jour. Med. Research, xxiv, No. 1.
3. Lieb: Immunity Production in Rabbits, etc., Jour. Med. Research, xxii, No. 1.
4. Römer: Ueber intrakutane Tuberculinanwendung, Beitr. z. Klin d. Tuberk., 1909, xii, 182.

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TABLE 1.—MEASUREMENT OF SKIN-FOLD

On June 3, 1910, each animal received 0.02 mg. O. T. intradermally.

Skin-fold measured before inoculation		48 hrs. later	Skin-fold measured before inoculation		48 hrs. later	Skin-fold measured before inoculation		48 hrs. later
No.	mm.	mm.	No.	mm.	mm.	No.	mm.	mm.
1....	1.40	1.52	5....	1.27	1.40	9....	1.78	1.78
2....	1.78	1.78	6....	1.78	1.78	10....	1.78	1.90
3....	1.78	1.78	7....	1.40	1.52	11....	1.78	1.78
4....	1.78	1.78	8....	1.78	1.90	12....	1.27	1.40

Reactions therefore considered negative.

In addition, the conjunctival test was also applied on June 1, 1910, one drop of 2 per cent. O. T. (Alexander's) in 0.9 per cent. sodium chlorid was instilled into the left eye of each monkey.

The next day nothing abnormal was noted in any of the conjunctivæ. June 3 conjunctivæ were normal.

When we were satisfied that the monkeys were probably not already infected with tuberculosis, we started inoculations with the living virulent human tubercle bacilli, June 8, 1910, and the following plan indicates how each animal was to be treated:

1. Control.
2. 25 bacilli in one dose and no further inoculations.
3. 100 bacilli in one dose and no further inoculations.
4. 200 bacilli in one dose and no further inoculations.
5. Increase slowly, 1, 3, 5, 10, 15, 20 bacilli, etc.
6. Increase slowly.
7. Increase rapidly, 1, 5, 10, 20, 50, 100 bacilli, etc.
8. Increase rapidly.
9. Increase slowly, 5, 10, 15, 20, 25, 30 bacilli, etc.
10. Increase rapidly, 5, 15, 45, 75, 125, 200 bacilli, etc.
11. Control.
12. 50 bacilli at one dose and no further inoculations.

The culture used in the following work was isolated Jan. 19, 1909, by Professor M. A. Barber with the aid of antiformin. The patient, from whom it was isolated, died of pulmonary tuberculosis a few days later.

On account of scarcity of guinea-pigs, we were not able to test the virulence of the culture on guinea-pigs until May 22, 1911. At this time Guinea-pig 1, weight 744 gm., received a subcutaneous inoculation of 35 bacilli; Guinea-pig 2, weight 575 gm., received 75 bacilli; Guinea-pig 3, weight 723 gm., received 125 bacilli.

All these pigs were killed a few weeks later and found to be infected with active tuberculosis.

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After five months had elapsed since the previous tuberculin inoculations, the monkeys were again tested by the Römer method.

TABLE 2.—DATES OF INOCULATIONS AND THE NUMBERS OF BACILLI INOCULATED

Date	Monkeys Nos. 5 and 6 Each No. of bacilli	Monkeys Nos. 7 and 8 Each No. of bacilli	Monkey No. 9 No. of bacilli	Monkey No. 10 No. of bacilli
6/ 8/10.....	1	1	5	5
6/15/10.....	3	5	10	15
6/23/10.....	5	10	15	30
6/30/10.....	10	20	20	50
7/ 7/10.....	15	50	25	75
7/14/10.....	20	125	30	105
7/28/10.....	30	300	40	150
8/ 4/10.....	40	450	55	200
8/11/10.....	50	700	70	250
8/18/10.....	65	1,000	90	325
9/ 7/10.....	80	1,500	115	400
9/17/10.....	100	2,000	140	500
10/ 6/10.....	125	2,800	175	600
10/15/10.....	150	4,000	185	700
10/20/10.....	175	5,500	215	800
10/28/10.....	200	7,000	250	900
11/ 4/10.....	225	9,000	300	1,000
11/11/10.....	250	11,000	350	1,100
11/17/10.....	275	13,500	400	1,200
11/25/10.....	300	15,000	450	1,300
12/ 1/10.....	350	18,000	550	1,500
12/ 8/10.....	400	21,000	650	1,700
12/15/10.....	450	25,000	750	2,000
12/22/10.....	500	30,000	850	2,400
12/29/10.....	550	35,000	1,000	2,800
1/ 5/11.....	600	40,000	1,200	3,300
1/12/11.....	700	50,000	1,500	4,000
1/19/11.....	800	60,000	1,800	4,800
1/27/11.....	900	65,000	2,100	5,600
2/ 3/11.....	1,000		2,400	

TABLE 3.—ROEMER TEST, APPLIED AFTER FIVE MONTHS

On Nov. 17, 1910, each animal received 0.05 mg. O. T. intradermally.

No.	Before inoculation mm.	48 hrs. afterward mm.	No.	Before inoculation mm.	48 hrs. afterward mm.	No.	Before inoculation mm.	48 hrs. afterward mm.
1....	1.8	1.8	5....	1.8	2.20	9....	2.29	2.29
2....	3.05	3.05	6....	2.29	2.54	10....	2.03	2.29
3....	2.54	2.92	7....	2.54	2.67	11....	1.78	2.03
4....	1.8	1.8	8....	2.54	2.54	12....	1.8	2.03

Reactions therefore considered negative.

Two and a half months later, the weekly living bacilli inoculations still being continued, the Römer test was again applied (Table 4).

It appeared from these tests that Monkeys 8, 10 and 11 must be infected, having given in their skin-fold measurement a percentage increase of 75 and over. The

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amount 20 mg. was unusually large and was given by mistake. Monkey 11, a control, was now killed and careful search was made for the presence of tuberculosis. Smears were made from the bronchial, mesenteric and inguinal lymph-glands and stained by the Ziehl-Nielsen and Gram methods. No tubercle bacilli could be found. Portions of the glands were macerated and injected into a guinea-pig, Feb. 10, 1911. This pig was tested intradermally, April 9, 1911, with 20 mg. Old Tuberculin. No reaction.

TABLE 4.—ROEMER TEST APPLIED AFTER SEVEN AND A HALF MONTHS

On Jan. 30, 1911, each animal was given 20 mg. O. T. intradermally.

No.	Before inoc. mm.	24 hrs. after mm.	48 hrs. later mm.	Percentage increase
1	1.78	2.29	2.54	42
2	2.41	3.05	3.05	26
3	2.29	2.54	2.54	10
4	1.70	2.03	2.29	33
5	1.90	2.03	2.15	13
6	2.34	2.54	2.79	19
7	2.23	2.67	2.54	19
8	2.03	3.29	3.72	83
9	1.52	2.29	2.15	50
10	1.78	2.48	3.17	78
11	1.52	2.67	2.48	75
12	1.78	2.03	2.03	14

May 28, 1911, the guinea-pig was killed. Necropsy showed no evidence of tuberculosis. From the fact that Monkey 11 was proved to have had no infection with tuberculosis it would seem that the positive intradermal reactions were a result of tuberculoprotein hypersensitiveness. Monkeys 7 and 8 were again tested, May, 1911, with 20 mg. Old Tuberculin intradermally. No reactions followed. The conjunctival test was again applied as follows:

May 25, 1911. One drop of 2 per cent. O. T. (Cutter's) in 9 per cent. sodium chlorid instilled into the right eye of each monkey.

May 26. No change.

May 27. No change.

It was now decided to give the remaining monkeys a subcutaneous injection of 5 mg. Old Tuberculin and to watch the temperatures resulting. The work of White

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and Fox[5] was carefully followed and the accompanying temperature curves show no increase of temperature following the injection of the tuberculin.

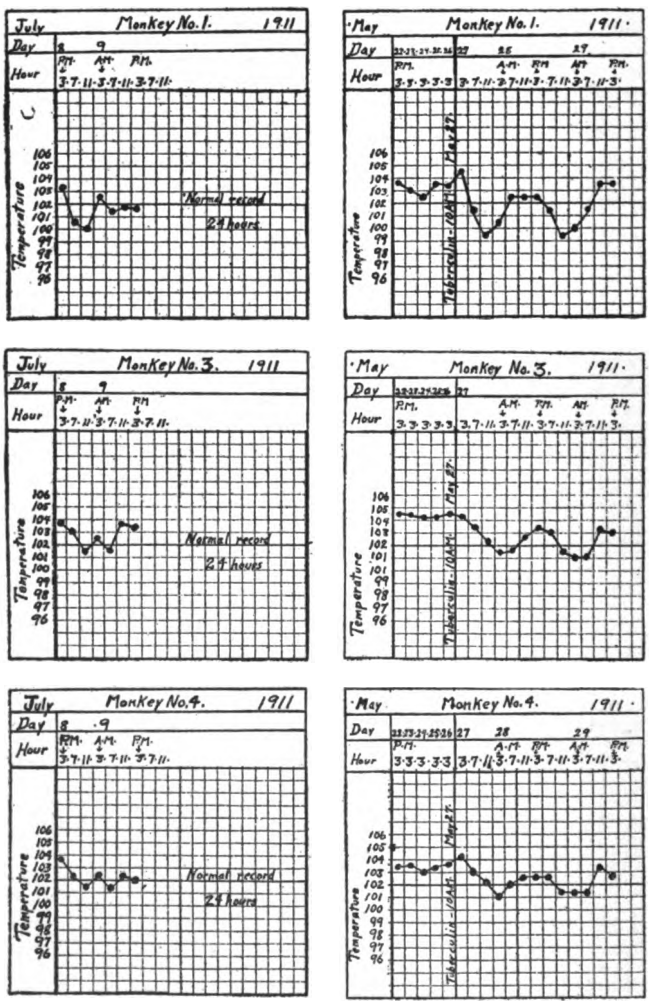

Fig. 1.—Temperature charts for Monkeys 1, 3 and 4.

It will be noticed in the table of Monkey 2 that a severe night drop occurred on the second day and the

5. White and Fox: Observations on Monkeys After Injections of Koch's Old Tuberculin, Tr. VI, Internat. Cong. of Tuberc.

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monkey became so ill it was thought he would die. He recovered the next day, but it was decided to kill him and also Monkey 8, which had received such large doses.

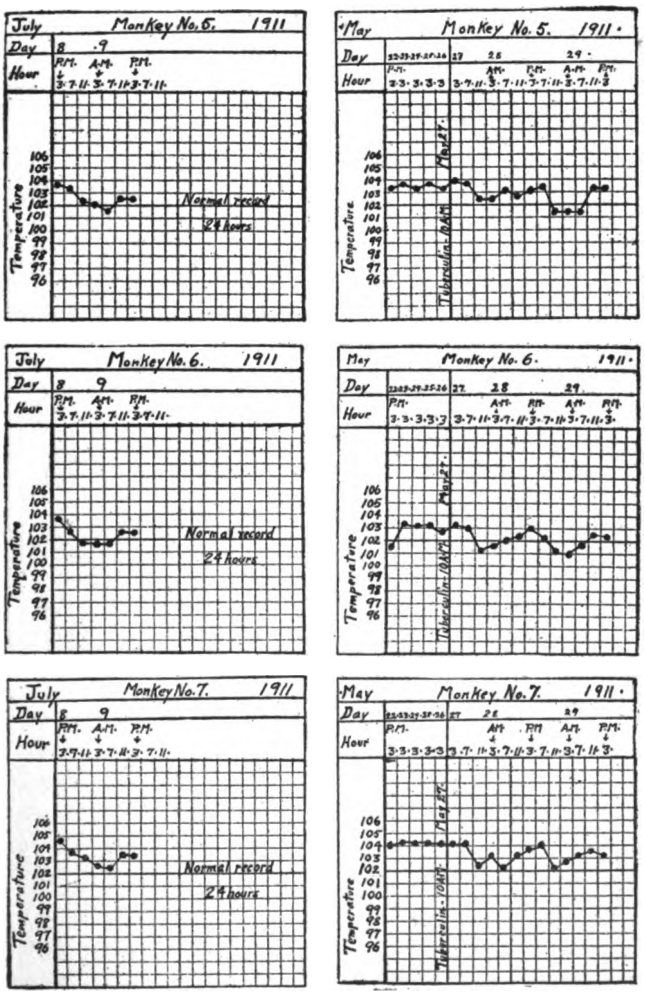

Fig. 2.—Temperature charts for Monkeys 5, 6 and 7.

The autopsies of these monkeys gave no evidence of tuberculosis. Smears were made from a large number of lymph-nodes and stained by Ziehl-Nielsen and Gram

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methods. No tubercle bacilli could be found. Portions of their lungs, lymph-nodes, spleen, liver and kidneys were macerated and injected into guinea-pigs. The

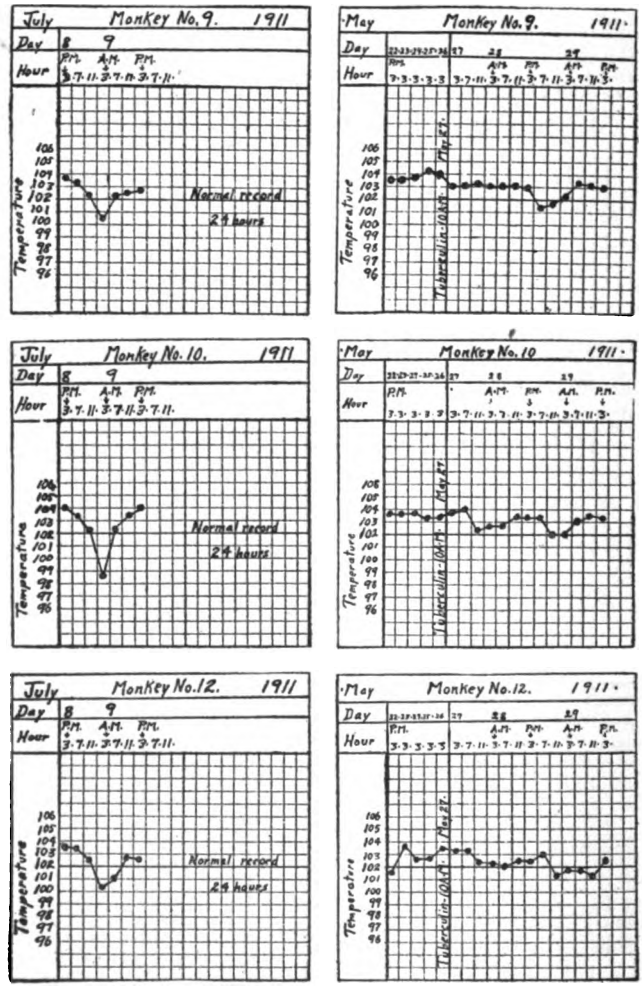

Fig. 3.—Temperature charts for Monkeys 9, 10 and 12.

guinea-pigs showed no evidence of tuberculous infection at autopsy. Portions of the macerated organs were treated with antiformin, but no tubercle bacilli could be found.

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The feces of each animal were twice examined by the antiformin method for tubercle bacilli; none, however, could be found. The normal night drop of a healthy monkey is well shown in the case of Monkey 1. It will be noticed that some interference with this night drop following the injection of the 5 mg. Old Tuberculin seems to have occurred in some of the monkeys. This may be due to the presence of specific antibodies or to tuberculoprotein hypersensitiveness as also the curious effect on Monkey 2 may have been.

Antibodies in the serums of the monkeys were tested for by means of the meiostagmin reaction described by Ascoli[6] and Izar.[7] This reaction depends on the decrease in surface tension which occurs when the specific antibodies in serum unite with the appropriate antigen when incubated together. The surface tension is accurately measured before and after incubation by means of the stalagmometer of Traube.

We prepared the tubercle antigen from the same culture used in the inoculation of the monkeys, following the direction of Izar and Ascoli.

The monkey serum was obtained in large quantities by dissecting out the jugular vein under chloroform anesthesia.

The serum from Monkey 2 representing an almost normal monkey and the serum from Monkey 8 representing an animal that had received excessively large doses of tubercle bacilli, both gave negative results. The test was applied June, 1911.

Emery's[8] method for measuring quantitatively the specific antibodies in a given serum was also made use of.

The test is an application of the Bordet-Gengou phenomenon. When the antibodies combine with the appro-

6. Ascoli: The Meiostagmin Reaction, München. med. Wchnschr., Jan. 11, 1910.
7. Izar: München. med. Wchnschr., April 19, 1910.
8. Emery: Immunity Reaction in Diagnosis, Lancet, Feb. 25, 1911.

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priate antigen, complement is extracted and hemolysis prevented. Emery has suggested a means of measuring the time necessary for complete absorption of complement which he terms the absorption time, and he uses it as an index of the amount of antibody present. In general the more antibody present the shorter the absorption time.

For carrying out the test we followed the technic of Emery and used (1) a sterile emulsion of tubercle bacilli in normal saline, from the same culture used in the inoculations; (2) fresh serum collected in a Wright's capsule from the ear of each monkey; (3) an emulsion of sensitized red corpuscles. This consisted of one part

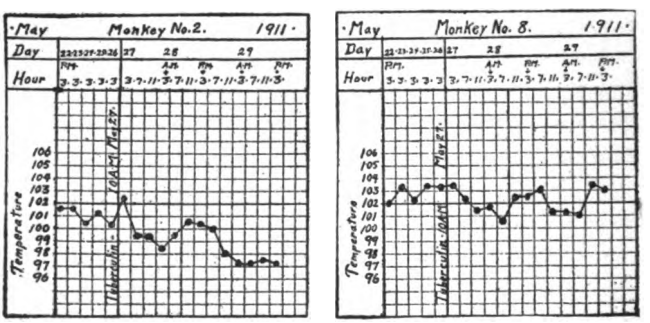

Fig. 4.—Temperature charts for Monkeys 2 and 8.

washed human corpuscles added to four parts of immune serum. The immune serum was obtained from a rabbit which had been repeatedly injected with well-washed human red corpuscles. The use of the red corpuscles of the monkey for injecting the rabbit would have been better. Our work thus far seems to show that monkey serum has a natural amboceptor for the red corpuscles of some people, so we may avoid the use of rabbits' immune serum in future tests.

Serums from Monkeys 1, 2, 7 and 8 were tested in the manner suggested by Emery and failed to show any complement deviation, the absorption time being prolonged in each instance. The tests were made in June, 1911, after inoculations had ceased.

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As yet we have made no attempt to demonstrate other possible antibodies.

Differential leukocyte counts were made as Tables 5 to 16 indicate. The total leukocytes of monkeys per c. mm. average about 15,000. The differential counts were made from blood obtained when the animals were fasting.

TABLE 5.—DIFFERENTIAL LEUKOCYTE COUNT, MONKEY 1

Date	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Large Mononuclears	Transitionals	Total Mononuclears	Eosinophils	Mast-Cells
1/23/11.....	27.5	40.5	28.5	3.5	0	(72.5)	0	0
1/30/11.....	18.5	37.5	44	0	0	(81.5)	0	0
2/10/11.....	19	36	45	0	0	(81)	0	0
2/21/11.....	30	36.5	31	1.5	0	(69)	1	0
3/ 4/11.....	15.5	34.5	45.5	3.5	1	(84.5)	0	0
3/20/11.....	15.5	25	57.5	2	0	(84.5)	0	0
4/ 3/11.....	9	37.5	51.5	2	0	(91)	0	0
4/17/11.....	10	3	87	0	0	(90)	0	0

TABLE 6.—DIFFERENTIAL LEUKOCYTE COUNT, MONKEY 2

Date	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Large Mononuclears	Transitionals	Total Mononuclears	Eosinophils	Mast-Cells
1/23/11.....	30	42	26	1	0	(69)	0	0
1/30/11.....	21	30	47.5	0	.5	(78)	0	0
2/10/11.....	33	8	53.5	3	2	(66.5)	5	0
2/21/11.....	22.5	21	52	2.5	2	(77.5)	0	0
3/ 4/11.....	26.5	6.5	55.5	10.5	1.5	(74)	0	0
3/20/11.....	19.5	14	59	5	2.5	(80.5)	0	0
4/ 3/11.....	30	43	25.5	.5	1	(70)	0	0
4/17/11.....	27.5	23.5	47	.5	1.5	(72.5)	0	0

TABLE 7.—DIFFERENTIAL LEUKOCYTE COUNT, MONKEY 3

Date	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Large Mononuclears	Transitionals	Total Mononuclears	Eosinophils	Mast-Cells
1/23/11.....	20	23	53.5	3.5	0	(80)	0	0
1/30/11.....	15	33	48	3	.5	(84.5)	.5	0
2/10/11.....	16.5	27	56	.5	0	(83.5)	0	0
2/21/11.....	17.5	32.5	47.5	0	2	(82.5)	.5	0
3/ 4/11.....	13.5	25.5	50.5	9	1.5	(86.5)	0	0
3/20/11.....	12	20	66.5	1.5	0	(88)	0	0
4/ 3/11.....	10	10	77.5	1	1.5	(90)	0	0
4/17/11.....	15.5	34	50.5	0	0	(84.5)	0	0

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TABLE 8.—DIFFERENTIAL LEUKOCYTE COUNT, MONKEY 4

Date	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Large Mononuclears	Transitionals	Total Mononuclears	Eosinophils	Mast-Cells
1/23/11.....	41.5	14	43	1	0	(58)	5	0
1/30/11.....	44	14.5	41.5	0	0	(56)	0	0
2/10/11.....	31	1	61	4	.5	(66.5)	2	0
2/21/11.....	25	23.5	46.4	4.5	.5	(75)	2	0
3/ 4/11.....	29.5	29.5	37.5	1.5	2	(70.5)	0	0
3/20/11.....	29	14.5	55.5	1	0	(71)	0	0
4/ 3/11.....	35.5	11.5	51	1.5	.5	(64.5)	0	0
4/17/11.....	35	1.5	63.5	0	0	(65)	0	0

TABLE 9.—DIFFERENTIAL LEUKOCYTE COUNT, MONKEY 5

Date	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Large Mononuclears	Transitionals	Total Mononuclears	Eosinophils	Mast-Cells
1/23/11.....	35.5	27	36	1	0	(64)	0	.5
1/30/11.....	36.5	27.5	35	0	0	(62.5)	1	0
2/10/11.....	37	32	30	.5	0	(62.5)	0	.5
2/21/11.....	36	23	39.5	0	.5	(63)	.5	0
3/ 4/11.....	30	17	47.5	4	1.5	(70)	0	0
3/20/11.....	36.5	43.5	20	0	0	(63.5)	0	0
4/ 3/11.....	23	16	59	2	0	(77)	0	0
4/17/11.....	29.5	14	54.5	0	0	(69.5)	0	0

TABLE 10.—DIFFERENTIAL LEUKOCYTE COUNT, MONKEY 6

Date	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Large Mononuclears	Transitionals	Total Mononuclears	Eosinophils	Mast-Cells
1/23/11.....	33.5	28	37.5	.5	0	(66)	0	.5
1/30/11.....	55.5	19.5	25	0	0	(45.5)	0	0
2/10/11.....	21	16.5	58	3	1	(78.5)	.5	0
2/21/11.....	51.5	1	45.5	.5	1.5	(48.5)	0	0
3/ 4/11.....	48	18	30.5	2	1.5	(52)	0	0
3/20/11.....	32	19	49	0	0	(68)	0	0
4/ 3/11.....	40.5	5	51	3	0	(59)	.5	0
4/17/11.....	28	14.5	56.5	1	0	(72)	0	0

TABLE 11.—DIFFERENTIAL LEUKOCYTE COUNT, MONKEY 7

Date	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Large Mononuclears	Transitionals	Total Mononuclears	Eosinophils	Mast-Cells
1/23/11.....	25	22.5	52	.5	0	(75)	0	0
1/30/11.....	47	25	28	0	0	(53)	0	0
2/10/11.....	30	9	50.5	2	1.5	(63)	7	0
2/21/11.....	31	7.5	55.5	4	1	(68)	1	0
3/ 4/11.....	14	27	57	1.5	.5	(86)	0	0
3/20/11.....	31.5	18.5	48.5	1.0	.5	(68.5)	0	0
4/ 3/11.....	19	1.5	76.5	2	.5	(80.5)	.5	0
4/17/11.....	26	18	56	0	0	(74)	0	0

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TABLE 12.—DIFFERENTIAL LEUKOCYTE COUNT, MONKEY 8

Date	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Large Mononuclears	Transitionals	Total Mononuclears	Eosinophils	Mast-Cells
1/23/11.....	27	29.5	42	1	0	(72.5)	0	.5
1/30/11.....	42.5	24	33	0	0	(57)	.5	0
2/10/11.....	28	38	32	1	1	(72)	0	0
2/21/11.....	32	2	63	1	1	(67)	1	0
3/ 4/11.....	24.5	21	52.5	2	0	(75.5)	0	0
3/20/11.....	20	21.5	58	0	.5	(80)	0	0
4/ 3/11.....	25	16.5	57.5	1	0	(75)	0	0
4/17/11.....	25	16	56	3	0	(75)	0	0

TABLE 13.—DIFFERENTIAL LEUKOCYTE COUNT, MONKEY 9

Date	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Large Mononuclears	Transitionals	Total Mononuclears	Eosinophils	Mast-Cells
1/23/11.....	33	34	33	0	0	(67)	0	0
1/30/11.....	46	33	21	0	0	(54)	0	0
2/10/11.....	30.5	42.5	27	0	0	(69.5)	0	0
2/21/11.....	32	16	46.5	4	1.5	(68)	0	0
3/ 4/11.....	32.5	10.5	50.5	6	.5	(69.5)	0	0
3/20/11.....	24	8.5	59.5	1	1.5	(70.5)	0	0
4/ 3/11.....	40	4.5	53	2.5	0	(60)	0	0
4/17/11.....	22.5	53.5	22.5	0	.5	(76.5)	1	0
4/21/11.....	26.5	4.5	68	0	0	(72.5)	1	0

TABLE 14.—DIFFERENTIAL LEUKOCYTE COUNT, MONKEY 10

Date	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Large Mononuclears	Transitionals	Total Mononuclears	Eosinophils	Mast-Cells
1/23/11.....	46	18.5	35	0	.5	(54)	0	0
1/30/11.....	39	17.5	43	0	.5	(61)	0	0
2/10/11.....	34	26.5	39	.5	0	(66)	0	0
2/21/11.....	40	12	44.5	3	.5	(60)	0	0
3/ 4/11.....	31.5	18.5	43	5.5	1.5	(68.5)	0	0
3/20/11.....	23	27.5	49.5	0	0	(77)	0	0
4/ 3/11.....	29.5	0	70.5	0	0	(70.5)	0	0
4/17/11.....	29	20	50	.5	0	(70.5)	.5	0

TABLE 15.—DIFFERENTIAL LEUKOCYTE COUNT, MONKEY 11

Date	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Large Mononuclears	Transitionals	Total Mononuclears	Eosinophils	Mast-Cells
1/23/11.....	34	24.5	40	1	1	(66)	0	0
1/30/11.....	30	36.5	33.5	0	0	(70)	0	0
2/10/11.....	33.5	17	47	2.5	6	(66.5)	.	.

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TABLE 16.—DIFFERENTIAL LEUKOCYTE COUNT, MONKEY 12

Date	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Large Mononuclears	Transitionals	Total Mononuclears	Eosinophils	Mast-Cells
1/23/11.....	36	29.5	34.5	0	0	(64)	0	0
1/30/11.....	45	13	39.5	.5	0	(53)	21	0
2/10/11.....	21	13	64	1	0	(78)	1	0
2/21/11.....	28	14.5	51	3.5	2	(71)	1	0
3/ 4/11.....	29.5	16	53	1	.5	(70.5)	0	0
3/20/11.....	40.5	6	51.5	.5	.5	(58.5)	1	0
4/ 3/11.....	30.5	19	49.5	.5	.5	(69.5)	0	0
4/17/11.....	36.5	8	54	1.5	0	(63.5)	0	0

We have shown[9] that differential leukocyte counts are of some value in indicating the degree of tubercle infection. It will be seen from Tables 4 to 15 that no evidence of infection can be deduced.

Judged by the high percentage of lymphocytes, and also from their dentition, the monkeys were young animals.

It must be remembered that the high percentage of lymphocytes which persist may be due to the altitude.[9]

Table 17 shows the increase in weight from the start up to the present time:

TABLE 17.—INCREASE IN WEIGHT

Weight in Grams

Monkey	June 8 1910	Nov. 17 1910	Dec. 5 1910	Feb. 3 1911	Feb. 10 1911	Mar. 14 1911	Apr. 10 1911	May 12 1911	July 8 1911
1..	2,381	3,430	3,402	3,316	3,387	3,416	3,373	3,345	3,345
2..	2,119	2,950	3,232	3,175	3,160	3,416	3,458	3,359	3,345
3..	2,920	4,340	3,997	3,940	3,897	3,714	4,266	4,196	4,457
4..	2,332	2,977	3,005	2,863	2,990	3,061	3,077	3,018	3,014
5..	2,296	2,580	3,033	2,891	2,778	2,905	2,976	2,990	2,958
6..	3,005	3,065	2,948	2,778	2,976	3,004	2,976	2,990	3.015
7..	2,381	3,090	2,778	2,863	2,863	2,877	2,919	2,920	2,892
8..	2,410	3,260	3,459	3,203	3,302	3,359	3,373	3,443	3,487
9..	2,532	3,065	3,515	3,316	3,260	3,345	3,401	3,499	3,665
10..	2,693	3,490	3,515	3,430	3,365	3,416	3,387	3,387	3,572
11..	1,935	2,470	2,575	2,521	2,579	....	....	....	....
12..	2,658	3,375	3,515	3,458	3,519	3,557	3,580	3,635	3,821

Two boys, G. R., aged 3 years, and W. R., aged 3 months, were first tested by means of the von Pirquet skin test and both were found to be negative. The father of these boys died a few weeks later of pulmonary

9. Webb and Williams: Some Hæmatological Studies in Tuberculosis, Tr. Nat. Assn. for the Study and Prevention of Tuberc., 5th annual.

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tuberculosis and the mother gave evidence of slight tubercle activity in one lung, accompanied by irregular temperature.

The children were inoculated with bacilli from culture B.[2] as indicated by the following figures:

TABLE 18.—NUMBER OF BACILLI INJECTED

Date	No. bacilli	Date	No. bacilli	Date	No. bacilli
10/20/10.....	1	11/25/10.....	18	12/29/10.....	100
10/27/10.....	3	12/ 1/10.....	25	1/ 5/11.....	125
11/ 3/10.....	5	12/ 8/10.....	35	1/12/11.....	150
11/10/10.....	8	12/15/10.....	50		
11/17/10.....	12	12/22/10.....	75		

Total number bacilli received by each child, 607.

The children were now again tested by means of the von Pirquet skin test and again the reaction was negative. We realize the intradermal test might have been more thorough, but as our results suggest with this test in monkeys and, as Krause[10] reports, with this test in guinea-pigs that it would seem possible to sensitize to tuberculoprotein, it is perhaps fortunate that we did not employ it. The children have gained weight and are thoroughly healthy to date. May 22, 1911, after four months' freedom from inoculations, the children were again tested and found again to be negative to the von Pirquet reaction.

CONCLUSIONS

1. We have not yet ascertained the exact number of tubercle bacilli of the culture employed which will infect a rhesus monkey.

2. A rhesus monkey, weighing 2,332 gm., withstood infection when injected at one dose with more than six times the dose of human tubercle bacilli which caused tuberculosis in a guinea-pig weighing 744 gm.

3. Two monkeys each received safely virulent human tubercle bacilli enough to kill at least 12,000 full-grown guinea-pigs.

4. No antibodies so far have been satisfactorily demonstrated in the sera of the vaccinated monkeys.

10. Krause found the intradermic route capable of conveying marked sensitization to tubercle protein when the toxic injection was given by the postorbital route.

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5. The temperature charts indicate the possible presence of such antibodies which might be interfering with the normal night drops following the subcutaneous inoculation of Old Tuberculin for diagnostic purposes.

6. It would appear that it is possible by the intradermal inoculation of Old Tuberculin to sensitize the skin of a monkey to tuberculoprotein.

7. Two children, both of whose parents were tuberculous, have been successfully vaccinated with upwards of 600 virulent human tubercle bacilli, without infection being produced to date.

Our grateful thanks are due J. E. Fuller, A.B., of Colorado College, for a large amount of valuable assistance.

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ABSTRACT OF DISCUSSION

Dr. J. F. Hultgen, Chicago: Some time ago I was able to show that tuberculosis in its three stages has three different kinds of blood-pictures. In the incipient stage of tuberculosis I have found the two curves, i. e., the polynuclears and mononuclears, close together, and even overlapping. In the second, the toxic stage, we have a definite corresponding anatomic-pathologic substratum and a definite blood-picture. In the third stage there is mixed infection, and the total white curve rises with the advance of the disease. Dr. Webb has succeeded in immunizing two persons, who have kept their immunity for months. I think this immunity may extend even further, for this reason: All diseases followed by long immunity have a negative phase lasting a long time; at least that is true in the typhoid fevers. Why those diseases which are followed by long immunity should show this blood-cell production I do not know. Andrews of London has done some work in that direction. He believes that the incubation of typhoid infections is nothing but the extended negative phase of leukopoiesis with the polynuclears screened within the lung capillaries. That, however, has not been confirmed. Dr. Webb is on the right road and immunity from tuberculosis in animals, and presumably in the human, is not only possible but likely. I think he has taken the first step toward establishing a ground on which can be based the immunity from tuberculosis, which kills so few and makes so many sick; whose mortality is so small, and whose morbidity is so great. If a patient dies *with* tuberculosis, that is not saying that he dies *of* tuberculosis. As to whether he is in possession of a tuberculous infection is for us to decide, and I think Dr. Webb has made this easy.

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Dr. Roy E. Thomas, Phoenix, Ariz.: Dr. Webb says the mononuclears in his monkeys averaged about 70 per cent., and this increase he thought possibly was due to the altitude. Dr. Watkins of Phoenix has recently made some experiments which show that we have there in normal individuals a percentage of leukocytes higher than they have in Colorado Springs. I think that altitude might perhaps fail to explain the high percentage of mononuclears in monkeys at Colorado Springs. Dr. Webb did not infect any of his monkeys. May it not be possible that all of his monkeys were already immune to tuberculosis?

Dr. E. R. Le Count, Chicago: I am reminded by this report of instances in which tuberculosis apparently finds its chief soil in the bones, instances of generalized miliary tuberculosis, with fever and enlarged spleen and outbreaks of tuberculous osteomyelitis in different bones. In some such cases the patient's general health suffers but little and there is an apparent immunity on the part of tissues other than the bones. I do not make this comment to hint at the possibility of bone tuberculosis in the monkeys Dr. Webb examined, but to call attention to the habit, so to speak, that the bacillus has formed in such cases, of growing in bones. The other viewpoint I have already stated in suggesting an immunity for other parts of the body than bones.

Dr. M. P. Ravenel, Madison, Wis.: I had the pleasure of seeing these monkeys and of going over the work with Drs. Webb and Wilson. I am proud of the fact that America can claim credit for the bulk of the work done in the immunization of tuberculosis. While Dr. Webb was not born in this country, he has become an American citizen and it looks as if we were going to get at the root of the matter in America. There are two things in this work which are of interest to me: one is the lack of antibodies, or at least inability to demonstrate them. If we know anything about immunity it is that it depends on the production of antibodies. That is not true always but, generally speaking, we must believe that immunity is due to the production of antibodies. The second point of interest to me is the infection of human beings. We know Behring's theory, that human beings are inoculated with bovine tuberculosis in early life; and Calmette's idea, that those of us who retain our immunity to tuberculosis are those who have had a single large dose, not sufficient to overcome the organism, or repeated small doses so spaced as to allow complete recovery between doses; that those who remain healthy have been vaccinated and have become immune. The question comes up, how much of a dose must a person take to be overcome by tuberculosis? I hope Dr. Webb will further explain the lack of the antibodies.

Dr. Gerald B. Webb, Colorado Springs, Colo.: I take it that the question of altitude would come in in regard to the

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increased lymphocytes found by Dr. Thomas at Phoenix, for we have found even an altitude of 800 feet gives higher lymphocyte counts than does sea level. I am grateful to Dr. Le Count for mentioning the possible bone infection. It is most important and we will pay more attention to this possibility in the monkeys. I do not believe any tuberculous lesions are present in them anywhere to date. We realize how healthy and vigorous they are when we have to catch them. Replying to Dr. Ravenel's questions concerning antibodies: We have so far failed to demonstrate them unless the interference in the night drop of some of the monkeys following the tuberculin test indicates their presence. In a patient who gets well naturally from diphtheria or even tetanus, antibodies cannot be found in the blood. Antibodies are probably a second line of defense, whereas our inoculations have probably only increased the first line, or the physiologic defense. Our monkeys are now in their second season. They have been kept in small cages in a small room but with the windows open. This room is used for boot-cleaning. Upwards of fifty tuberculous invalids have been in the room at different times and part of the time the monkeys were cared for by a man with advanced pulmonary tuberculosis. As the charts indicate, the lymphocytes of these monkeys still remain high in spite of the monkeys becoming older. This is no doubt the result of the altitude as we have shown to be the case in other animals. As the lymphocyte is considered the natural antagonist of the tubercle bacillus, our work of inoculation with live bacilli has been done under the most favorable conditions on account of the increased numbers of these cells present at this altitude.

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SURGICAL PATHOLOGY OF THE PROSTATE

REVIEW OF 468 CASES *

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AND
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We have recently reexamined the specimens and reviewed the data from all cases of operations on the prostate in this clinic from Oct. 28, 1904, to June 1, 1911. The series, comprising as it does 468 cases, is large enough to warrant placing the observations on record for comparison with the conclusions of previous observers.

Since the publication of the studies of Young, Geraghty and Stevens in 1906, the only comprehensive memoir which has appeared is that of von Frisch, last year. Therefore, we have discussed elsewhere the subject of the prostate, some what at length, deeming it advisable to review therein the essential points in the anatomy and the physiology as well as the pathology of the gland. In thus adding to our own observations a somewhat full review of the data and discussions of others concerning the normal and the pathologic conditions of the prostate, we have hoped not alone to stimulate interest in this organ, but also to place in convenient form the more important facts and theories concerning it, as a basis for future studies. Herein we shall confine ourselves to a somewhat brief recital of the main points in our paper, referring the reader elsewhere for the more detailed discussion of them.

ANATOMY

During the third month of fetal life the mesoblastic tissue surrounding the lower ends of the Müllerian and

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Wolffian ducts becomes differentiated in association with a thickening of the wall of the primitive urethra. Simultaneous with this the epithelium of the sinus urogenitalis throws off three groups of buds (Pallin) on each side. These buds consist initially of solid cordons of epithelial tissue which penetrate into the annular mass of mesoblastic tissue surrounding them. The glands do not acquire a lumen until after birth.

Shape. — The prostate is, geometrically, an oblate conoid, flattened dorsoventrally, with its base upward and its apex resting on the triangular ligament. The transverse diameter is usually 1/5 to 1/4 more than the base-to-apex diameter of the gland.

Weight.—For comparative purposes, all adult prostates weighing under 16 gm. may be considered abnormally small, all weighing from 16 to 24 gm. normal in size, and all weighing 24 gm. or more as abnormally increased in size.

Subdivisions.—From the posterior aspects the prostate is a bilobular bilaterally symmetrical organ. In its posterior border is a notch, from which a palpable groove extends to the apex, marking the course of the urethra. The slightly convex lateral lobes lie to the right and left of this groove.

In our unabridged article we have discussed rather in detail and presented the illustrations of Tandler and Zuckerkandl's recent contribution on the important question of prostatic hypertrophy. In an especially adapted and extensive series of cases these investigators have demonstrated that hypertrophy of this gland always begins in the *middle lobe,* that total hypertrophy never exists, since atrophy is also present, and that the *surgical capsule* is composed of prostatic tissue. Consequently, prostatectomy is an *intraprostatic* procedure. Based on their observations, which showed that the hypertrophy always involved the portion of the prostate toward the bladder, Tandler and Zuckerkandl hold that

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operation through the bladder-route is the method of choice. A description of the technic from the anatomist's standpoint is also given.

The verumontanum, or colliculus seminalis, is a long elevation, about 3 mm. high, composed mostly of cavernous tissue and situated near the middle of the posterior wall of the pars prostatica urethræ. It declines at both ends, and on its anterior reclivity is a fine slit-like opening, the exit of the uterus masculinus.

The uterus masculinus is a pear-shaped, longitudinal pouch, extending upward and backward to the base of the prostate, and ending between the ejaculatory ducts. Normally it is 10 to 12 mm. in length, lined with mucous membrane and surrounded by a circular layer of muscle.

The ejaculatory ducts, which transmit the secretion of the seminal vesicles, pass obliquely through the prostate from above, opening into the pars prostatica urethræ dividing it into a proximal and distal portion.

Relations.—From a pathologic standpoint the more important relations of the prostate are the following: (a) the base is in intimate contact with the floor of the bladder; (b) the posterior surface is separated from the rectum by only sparse tense, cellular tissue, poor in fat; (c) the body of the gland embraces a considerable portion of the urethra (pars prostatica urethræ); (d) it communicates with the seminal vesicles and the ejaculatory ducts; (e) it likewise communicates through the vas deferens with the epididymis and the testicles.

Structure.—The prostate possesses a fine fibromuscular capsule of its own which is firmly adherent. It completely invests the gland, and sends a median septum inward, which surrounds the urethra and gives off a number of thinner partitions which divide the parenchyma of the gland into about forty lobules.

In addition, the organ is fixed in its position by fibrous tissue which has been designated by A. Retzius as the "ligamentum pelvio-prostaticum capsulare." This pos-

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sesses partly the form of an envelope and partly the structure of band-like strips spreading into the enveloping portion and connecting the prostate with the pubis (the ligamentum puboprostaticum).

The visceral layer of the pelvic fascia, first described by Desnonvillers, is lifted up from the pelvic fascia laterally and posteriorly, appears as an application—Waldeyer—of this fascia, on the prostate. From this it passes over the bladder, enclosing the upper surfaces of the plexus pudendalis, the plexus vesicoprostatici, the seminal vesicles, and the ampulla of the ductus deferentes. Between the rectum and the prostate the sapsule is strongest.

The muscular element of the prostate is made up of unusually fine, unstriated fibers. The second sphincter muscle (sphincter vesicæ [Henle], sphincter prostaticus [Kohlrausch]) is formed of striated as well as smooth muscle-fibers. Striped muscle-fibers also pass between the two sphincters on the anterior surface of the prostate. In the interior of the gland the muscular element is a dense fibromuscular mass surrounding the urethra. Through this mass pass the prostatic ducts. Spreading out from it in all directions are muscular bands consisting of transverse and longitudinal fibers. While these usually follow the connective tissue framework, in many places they form by themselves the interalveolar septa without admixture with any discernible fibrous tissue. Here and there they form circular or looped structures which embrace the gland lobules. Frisch holds that it is the smooth muscle of the prostate proper which forms the sphincter vesicæ internus.

The parenchyma of the prostate consists of from fifteen to thirty-two distinct glandular systems, each opening by an independent excretory duct into the urethra. Some anatomists describe these gland units as terminal and others as an alveolar type. The terminal alveoli are found scattered throughout the gland, so that a section at any level shows both alveoli and ducts.

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We have never seen a tunica propria about any of the alveoli, which agrees with the observations of other recent workers. Instead, the epithelium rests directly on the smooth muscle or fibrous connective tissue.

While in the alveoli of the adult prostate a double layer of epithelium is frequently encountered, it is an open question whether such a formation is normal or not. Langerhans says: "In all alveoli a double layer of cylindrical epithelium is present."

The cylindrical epithelium lines the glands throughout except near the orifices of the ducts where transitional epithelium similar to that of the urethra is present.

Islands of lymphoid tissue are not infrequently found in the prostate. Weski, who has carefully studied these, notes their analogy to those found by Waldeyer in the dog's prostate. He mentions the possibility that the structures may be pathologic, but believes, on account of the entire absence of other evidences of inflammation in the same glands, and on account of the known presence of similar lymph follicles in other glands, that they may be considered physiologic.

The arteries arise principally from the inferior vesical artery. A few small branches also arise from the middle hemorrhoidal and internal pudendic arteries. They enter the periphery at numerous points, penetrate the gland and divide, forming a close capillary meshwork within the alveolar walls.

The veins form a rich plexus within the gland tissue and around the ducts. They emerge from the organ laterally and pass in part into the rich plexus within the capsule, and in part beneath the mucous membrane in the region of the orificium internum and the colliculus seminalis. Bordering on the anterior surface of the prostate, behind the ligamentum arcuatum pubis and under the edge of the symphysis pubis is the plexus pubicus impar, which receives not only the blood from the prostate, but also from the deep dorsal veins of the

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penis, communicates with trunks from the bladder, seminal vesicles and rectum and is continued as the prostatovesical plexus to the internal iliac veins.

The lymphatics form a wide-meshed network on the surface of the gland. Within the organ they are richest at the base and most sparse at the apex. Compared with the blood-vessels their course is surprisingly tortuous. The lymphatic plexuses on each side form two trunks, a superior and a lateral. The superior pass to the obturator lymph-nodes of the pelvis and the lateral to the internal iliac lymph-nodes (Sappey). The endothelial cells of the lymphatics are characterized by a very finely granular protoplasm.

The nerves of the prostate take their origin from the inferior hypogastric plexus of the sympathetic. The organ is richly supplied with nerves and contains, chiefly on its periphery, ganglion nodes, numerous isolated ganglion cells and a great number of variously constructed end-organs. As a delicate plexus they pass from the seminal vesicles. In this plexus are present fibers from the anterior roots of the third and fourth sacral nerves.

The nerve end-organs on the outer surface of the prostate have been known for a long time. In the mucous membrane of the pars prostatica, von Planner has found numerous bulbous nerve-endings which are situated in the more superficial layer of the membrane and which are sometimes plainly visible as elevations. The recent elaborate and painstaking studies of Timofeew have shown that the prostate contains a most complicated system of nerve-fibers and nerve-endings.

PHYSIOLOGY

In order to appreciate the physiology of the prostate three points must be considered: first, its function as a secreting gland; second, its muscular apparatus, particularly the sphincter formation; and third, its extraordinary wealth in nerve-fibers, ganglion cells and nerve end-organs.

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As a secreting gland the prostate undoubtedly belongs to the sexual organs. The secretion of the prostate is a very essential factor of the spermatic fluid. Up to the time of puberty the gland undergoes a rapid growth and reaches its complete development only after that time. After the loss of the testicles in childhood the gland is arrested in its development; after castration of the adult it becomes atrophied.

Casper's work with dogs of the same litter showed that double-sided castration resulted in all cases in a marked diminution of the prostate and most decided changes in its glandular structure. Neusser notes that the persistence of the prostatic secretion, in many cases for a long time after castration, and the actual power of coition in the eunuch, which is lost only after years, indicate that an independent function must be attributable to the prostatic gland or to the innervating apparatus. Fürbringer has shown that the so-called "Böttcher" or "spermatic crystals" arise from the prostate. He succeeded in demonstrating the crystals by evaporation of the prostatic secretion secured from fifty-six autopsies (90 per cent.).

Besides the Böttcher crystals one finds constantly in the prostatic secretion large, colorless, moderately refractive, round granules. These produce the milky cloudiness and, judging by their reactions, consist chiefly of lecithin. The filtrate contains albumin but no mucin.

Spermatic crystals are not present in prostatic secretion secured by rectal palpation of the living. Ammonium phosphate, however, added to such expressed secretion causes the formation of the crystals. Fürbringer therefore concludes:

For the formation of the Böttcher crystals observed in the ejaculated spermatic fluid, the secretion of the prostate affords the basic portion, whereas the phosphoric acid necessary thereto is contributed by the other components of the spermatic fluid.

In the dead body the post-mortem degeneration of the epithelium probably furnishes the necessary phosphoric acid. The characteristic spermatic odor is probably an

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attribute of combinations of the Schreiner base in dissolved form. Fürbringer demonstrated that the secretion of the prostate causes the normally motionless spermatozoa, as they are stored in the seminal tract, to become motile.

The descriptions found in the literature of the appearance of the prostatic secretion as clear, glossy, thready, etc., are incorrect, as Fürbringer explained. The secretion is a thin fluid of milky cloudiness, slightly acid or neutral in reaction and of a highly characteristic odor.

Percy has shown that spermatozoa quickly die in contact with uterine mucosa without the admixture of prostatic secretion, while in the presence of this secretion they remain alive three to eight days. Steinach has pointed out that simultaneous extirpation of the seminal vesicles and the prostate, while not interfering with the power of copulation, nullifies the capacity of begetting.

That the prostate possesses an internal secretion which acts on the external secretion of the testicles, vas deferens and the seminal vesicles, is strongly suggested by the work of Serralach and Parès. They found that after the removal of the prostate from dogs the secretion of all the sexual glands ceased, spermatozoa were no longer to be found and the testicles became atrophied. When injections of glycerin extract of the prostate were made after the prostatectomy, atrophy of the testicles did not occur, ejection remained, and spermatozoa were demonstrable in the ejection.

The arrangement of the smooth muscles of the prostate, longitudinally about the glandular tubules and circularly about the alveoli, is such that their contraction empties the gland of its accumulated secretion. According to Lusena, the quantitative relation of the muscles and glands of the prostate varies according to the age of the individual. In middle life the muscles and glands are present in the same amount. In old age the muscles are developed at the expense of the glands. Between 25 and 30 years of age the genital activity of the prostate

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reaches its highest point. Between 45 and 50 years the fibromuscular layer becomes relatively more extensive, a sign of beginning age.

The mechanism of the bladder closure and the emptying of the urine may be properly ascribed to the sphincters of the prostate, Rehfisch and Posner to the contrary notwithstanding. The closure of the bladder is cared for by the smooth sphincter internus muscle which remains in a state of tonus. This tonus must relax when there is need to pass urine and then the effect of the detrusor muscle comes into action.

Frisch calls special attention to the fact that while the unstriated muscles of the internal sphincter may be the usual mechanism for closing the bladder, yet the auxiliary muscles of the perineum can assist in producing the same effect by an energetic voluntary contraction, a fact which is important in prognosis after prostatectomy.

It is probable also that the numerous ganglia situated in the prostate and bladder hold an important function in the closure of the latter and in urinary discharge, and that these must be looked on as centers.

In regard to the nerves of the prostate all the motor and vasomotor fibers in the nervi erigentes and nervi hypogastrici, which arise from the inferior mesenteric ganglion, reach the prostate. Stimulation of the erigentes has a negative result, or, in the beginning, the excretion of a considerable amount of secretion, which is then followed by a cessation. On the contrary, stimulation of the hypogastrici produces a continuous, genuine secretion. If a cannula be introduced into the urethra in connection with a long upright tube, the level of the fluid mounts rapidly upward through stimulation of the nervi erigentes and sinks again downward as soon as the stimulation is suspended. Under similar conditions, if the hypogastrici be irritated, then the entire tube becomes filled and the fluid flows out from above. The erigentes, therefore, only press the secretion out

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of the gland, which secretion has been produced by the stimulation of the hypogastrici, so that these are the real secretory nerves. Stimulation of the central stump of one of the hypogastrici, with its fellow intact, produces secretion, and does this even when the inferior mesenteric ganglion has been separated from the remaining sympathetic fibers and, consequently, separated also from the central spinal cord.

PATHOLOGY

INFECTIONS OF THE PROSTATE

1. Acute Prostatitis.
   - A. Catarrhal.
   - B. Follicular.
   - C. Parenchymatous.
   - (Segond's classification; also held by Guyon).
2. Chronic Prostatitis.

Etiology.—As idiopathic primary processes they are rare and, excepting as complications of gonorrhea, infrequent.

Causes attributed by various authors are: from without, injuries due to horseback riding, bicycle riding and similar exercises; from within, unsuitable introduction of instruments, too frequent and unclean catheterization, lithotripsy, abortive injections, too severe cauterization of the pars prostatica (especially with the pencil—Guyon), unnecessary duration of the self-retaining catheter, caught stones and foreign bodies, stricture of the urethra.

Disposing causes are: congestions and irritations in the rectum (hemorrhoids, foreign bodies, fissures, fistulas, proctitis and periproctitis), chronic obstipation, dysentery and enteritis, venereal excess, masturbation, coitus reservatus, metastases in pyemia, typhus, measles, small-pox, croupous pneumonia, parotiditis, influenza, tonsillitis, carbuncle, furuncle, phlegmonous angina, gout, syphilis, cystitis, stones in the bladder, prostatic hypertrophy, and infection by way of the blood.

By far the most frequent cause is gonorrhea. Prostatitis can follow not only every acute gonorrhea of the

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posterior urethra, but also every stage of chronic gonorrhea. The older the latter, the more frequently will the prostate be found diseased. Whereas the infection is usually from the posterior urethra, many admit its possibility from the anterior urethra—perhaps by way of the lymph channels. Opinions as to the frequency with which prostatitis follows gonorrhea vary within wide limits. These differences are explained as probably due to errors and difficulty in diagnosis; those holding high percentages including in their statistics the mild, but more frequent cases; and those quoting low percentages limiting their diagnoses to severe parenchymatous prostatitis alone. The weight of evidence, however, appears to favor the opinion that prostatitis is a frequent complication of gonorrhea.

In our series of 468 cases, seven were tuberculous. Tuberculosis of the prostate is principally a disease of the young adult, though our meager list of cases does not show it.

With regard to its etiology it is highly improbable that heredity is a predisposing cause, though it has been suggested by a number of observers. It is also unlikely that acute local hyperemia, or acute inflammations, as in sexual excesses, acute cystitis, etc., predispose to tuberculosis. Chronic inflammations, on the other hand, may do so. There is no basis for the supposition that direct infection may come from without. Infection takes place most frequently through the blood-stream. The well-known tendency of the prostate to exhibit evidences of infection in typhoid fever, glanders, etc., is analogous to the condition which probably obtains in tuberculosis, namely, that the organ is one in which even small amounts of bacilli circulated in the blood are caught and stored up. That the prostate may be the only organ of the body secondarily affected by tuberculosis is shown by the number of cases reported as permanently cured after prostatectomy.

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Secondary disease of the prostate may be developed from the epididymis or, more rarely, from the kidney or the seminal vesicles. Baumgarten and Krämer have shown that the extension of tuberculosis in the urogenital tract follows the stream of the secretions and rarely proceeds against the stream. It must be noted, however, that several portions of the urogenital system may be affected simultaneously and independently of each other through the blood-stream.

The tuberculous prostate is frequently more involved in one lateral lobe than in the other. The periphery of these lobes is the most frequent site of tuberculosis. In all of our cases the disease was confined to the lateral lobes and not in the neighborhood of the urethra.

Microscopically, the tubercle bacilli are usually demonstrable between the epithelial cells and in the borders of recent tubercles. Secondary infections are occasionally present, producing suppurative softening and abscess instead of ordinary caseation. Staphylococci and, more frequently, *B. coli communis* are usually the accessory pathogenic organisms. Halle and Motz hold that surgical interference should not be attempted in cases with acute secondary infection.

In case of infection from the intestine the microorganisms pass directly from the intestine through the inflamed wall into the prostate. Infection by way of the blood is to be assumed when a direct transmission from the urethra, from the intestine, and by way of the lymph-channels can be excluded. This holds for primary suppurative prostatitis as well as for the chronic form.

Acute Prostatitis.—The ordinary picture in text-books is misleading. These describe the symptoms of the severe parenchymatous type, making that the typical picture of acute prostatitis, whereas both the lighter forms, namely the catarrhal and the follicular, are much more frequent.

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A. Catarrhal Prostatitis: Acute gonorrheal catarrah of the prostatic gland is undoubtedly the most frequent form of acute prostatitis, and it is very likely that acute posterior urethritis cannot run its course without involving the gland. The gonococci pass quickly into the excretory ducts and produce a deep-seated process, involving prostatic glandules, utriculus, ejaculatory ducts, and even the seminal vesicles.

B. Follicular Prostatitis: This is developed as a rule from acute gonorrheal catarrh. It occurs frequently as a sequence of posterior urethritis, but can even be associated with chronic prostatitis. There is stagnation of the secretion, due to obstruction of the openings, and the process leads to the formation of abscesses. Jadassohn designates these as "pseudo-abscesses," since the suppuration exists in preformed cavities. The cut surface in the lateral lobe presents little points of thick pus.

C. Parenchymatous Prostatitis: This involves the entire gland. The lighter forms are designated as hyperemia or congestion of the prostate. The organ is doubly, even quadruply, enlarged, feels hard and tense. The blood-vessels on the surface are redundantly filled with blood. The cut surface of the prostate is more markedly reddened than in the healthy organ. On pressure there is expressed a reddish and somewhat cloudy fluid—a mixture of lymph and serum—arising from blood out of the filled capillaries, also from prostatic fluid and a small amount of pus, since one sees merely a few pus cells under the microscope.

Chronic Prostatitis. — Etiology: Guyon and Fürbringer consider chronic prostatitis a rare condition, whereas Finger, Frisch, Posner and several others hold that it is common.

Gonorrhea is the most frequent cause. Other causes mentioned are onania and other sexual excesses, stricture, cystitis—chiefly where ammoniacal urine is present —vesical and prostatic stones, catheterization and other traumata, and hypertrophy. Stern speaks of prostatic

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affections in diabetics and bases his opinion on the fact that, when such patients are placed on a diabetic diet the symptoms subside, to recur when the diet is again withheld.

In the case of gonorrheal prostatitis the striking changes take place almost always at the caput gallinaginis. This is either symmetrically or asymmetrically enlarged, its mucous membrane loosened and possesses here and there papillary excrescences, or is thickened like a cicatrix.

A point worthy of note is the fact that a genuine new formation of glandular tubules is to be observed on the glands in many cases, a point which, up to the present time, has been only superficially mentioned by Albarran. This glandular new formation is at times of such a kind that an adenomatous-like structure arises. However, there is always seen in the immediate vicinity inflammatory foci, often in very luxuriant growth and in direct communication with the real inflammatory center, so that there is no doubt of the causal relationship between the inflammation and the glandular development.

Hypertrophy.—Statistical Data: In our series of 468 prostatectomies, 387 cases (83 per cent.) were hypertrophy, the remainder being cases of tuberculosis or neoplasms. The ages of the patients whose prostates showed hypertrophy only were as follows by decades:

50 to 60 years of age	65	(17 per cent.)
60 to 70 years of age	194	(50 per cent.)
70 to 80 years of age	116	(30 per cent.)
80 to 90 years of age	12	(3 per cent.)

It will be seen from the above figures that all of the patients were above 50 years of age, and that 83 per cent. were above 60. Thus all the patients may fairly be assumed to have passed the most active period of sexual life. Of these patients, 78 per cent. were married, 18 per cent. were widowers and 4 per cent. were single.

Of our 387 cases, in only seventy was the parenchyma increased without apparent increase of the stroma. In

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but seventeen the stroma was increased without any apparent increase of the parenchyma, while in 300 cases there was increase of both stroma and parenchyma. In 205 of the cases the increase in the muscular element was sufficiently prominent to be noted. While, of course, these observations do not cover microscopically every portion of the gland removed, they have been made on sections selected in each case from a number of different areas.

In 266 cases there was present a round-cell infiltration either diffuse or somewhat circumscribed. In these cases it was usually impossible to say whether or not the round-cell infiltration was lymphoid or inflammatory tissue.

Etiology: With regard to the etiology of prostatic hypertrophy no hypothesis has yet been advanced adequately harmonizing the facts. Elsewhere we have discussed the various causes that have been cited by investigators, but such detail must be omitted here.

Whatever may be the initial stimulant or the broad biologic factor which lies at the base of the prostatic hypertrophy, we are inclined to think that the following steps represent the usual development of the disease.

1. There is an initial hyperplasia of the parenchyma, marked microscopically by high cylindrical epithelium with swollen nuclei, which resemble in all respects actively secreting epithelium in other well-studied glands. That these epithelial cells are actively secreting is further shown by the presence in early stages of relatively large amounts of secretion, which is distinguished grossly from that of the normal prostate. This parenchymatous hyperplasia is frequently so great as to result in the development of marked infoldings of, and papilliferous proliferation from the alveolar walls, sometimes carried to the extent of completely bridging the alveoli.

2. Apparently the second stage of hyperplastic development, though not a definitely limited one, is that of retention within the alveoli and tubules of the secretion.

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This retention may be due to beginning exfoliation of the epithelium, and it may be due in part to blocking of the excretory ducts of the individual gland-units by a beginning concomitant muscular hyperplasia.

3. The third stage is parenchymatous degeneration, which in the hypertrophied prostate is marked by atrophy or exfoliation of the epithelium. The first of these processes is shown by the flattening of the epithelial cells, the reduction in size of the nuclei, and the diffuse staining of their protoplasm. The second process, exfoliation, may and frequently does occur in epithelium which is still in the high columnar, secreting phase. Atrophic epithelium is usually associated with swollen cystic acini. Exfoliations occur in any acini, but are densest and best-preserved in large acini. Exfoliation may be so extensive as to present a picture of completely denuded alveoli or cyst-walls. The stripping of the epithelium from the papilliferous projections and alveolar bridges leaves these as slender, fibrous projecting or bridging structures.

4. Early in the development of parenchymatous hyperplasia there begins a muscular overgrowth which represents, apparently, an attempt on the part of Nature to expel from the gland the retained secretion. Our cases, however, do not show a large percentage in which the muscular hyperplasia greatly outweighs the element of fibrous connective-tissue overgrowth.

5. The overgrowth of fibrous connective tissue in the hypertrophied prostates in our cases is the most constant factor, though it must be borne in mind that many cases coming to operation may fairly be assumed to have long passed the stage of active parenchymatous and muscular hyperplasia. The fibrous connective tissue may well have its origin not alone in acting as a supporting frame-work for the increased glandular elements, but also in metaplasia of the smooth muscle-elements. In the normal prostate the muscular and fibrous connective tissue are so blended that it is readily conceivable that with over-

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growth and overfunction the unstriated muscle fiber may, by steps of gradual transition, change into fibrous connective tissue as a terminal stage in the life history of the muscle cell.

Tandler and Zuckerkandl state that the usual classification of the lobes from external form alone is incorrect. They hold that the lobes should be classified according to the zones of glandular distribution, which is supported by the embryology of the prostate. Thus considered the organ is divided into anterior lobe, middle lobe and two lateral lobes. The ducts of the anterior lobe open on the anterior urethral wall opposite the veru montanum, those of the middle lobe on the posterior wall of the urethra, proximal to the veru montanum, and the ducts of the lateral lobes are found on both sides of that elevation. The middle lobe lies between the urethra and the ejaculatory ducts, and, as recent anatomic examinations have demonstrated, is the starting point of prostatic hypertrophy.

Neoplasms. — The question that has seemed to us uppermost in the minds of physicians inquiring into the results of research on the prostate has been: "What is the percentage of malignancy?" Viewed in the light of a comparison between the statistics of recent investigators and those of the older writers, that question is decidedly pertinent.

The extremely limited recognition of malignancy in the prostate up to the time of Thompson's contribution in 1854, and the gradual increase in its recognition from that date to the present, are a stimulus to keener observation and study of the prostate with regard to neoplasms. Tanchou's statistics, compiled by Thompson, showed but five cases of prostatic cancer among 8,289 patients, who had died from cancerous disease. Among 548 cases of cancer in the Billroth clinic, von Winiwarter found only one case of prostatic cancer.

These figures sufficiently emphasize the extreme rarity of the recognition, in earlier days, of malignancy in the prostatic gland.

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In 1854 Thompson contributed the first available statistics on the subject, having cited eighteen cases from the English and the French literatures. In 1866 Wyss reported twenty-eight cases, including those of Thompson. Since that time other reports have been made as follows: Socin (1875), fifty cases; Kapuste (1855), 114 cases; Engelbach (1888), 114 cases; Wolff (1899), 110 cases. Young has reported sixty-eight carcinomata among 250 enlarged prostates, which had been extirpated. Belfield has made the observation that 10 per cent. of all hypertrophies are carcinomata. In our series of 468 cases there were seventy-three (15.5 per cent.) carcinomata. Sarcoma of the prostate is relatively rare. Kaufmann cited twenty-four cases, and eleven others have since been added to that number by various investigators. Although the statistics of some writers have shown a higher percentage than the above, a more exact examination of their material has not confirmed their figures, and indicate that Kaufmann's statistics are to be considered the basis for judgment as to the frequency of sarcoma in this gland.

In this brief historical review may be noted the steady advancement during the past half-century in our knowledge of malignant growths in the prostate. Although the statistics of recent investigators vary within somewhat wide limits as to frequency of its occurrence, yet it should be a generally recognized fact that carcinoma of the prostate is a comparatively frequent disease, and that sarcoma of the prostate, though relatively infrequent, does occur.

These neoplasms may be present in the gland both primarily and secondarily. Cancerous and sarcomatous nodules—the latter by far the more infrequent form—have been observed in cases in which the primary foci were situated in various organs. The primary tumor has been found most frequently in the rectum, less often in the urinary bladder, the seminal vesicles, on the penis, in the stomach (Engelbach), the lungs (Fenwick), and

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the dura mater. Kaufmann held genuine metastatic growths of the prostate to be extremely rare.

Malignancy in the prostate is observed from earliest childhood to late old age. Carcinoma is more prevalent in the latter decades of life, and sarcoma in the beginning years.

Of our patients

1 was between 40 and 50 years of age.
9 (12 per cent.) were between 50 and 60 years of age.
29 (40 per cent.) were between 60 and 70 years of age.
30 (41 per cent.) were between 70 and 80 years of age.

The middle period is relatively free from malignancy in this organ. The youngest patients observed were children 6, 8 and 9 months old (Rose, Socin, Bree). Since, undoubtedly, the beginning of development is to be dated much earlier, Klebs held as not unlikely that the process may at time be referred even to the intra-uterine period of life.

Pathologic Anatomy: Of the seventy-three cases, fifty-one (69 per cent.) showed marked glandular hypertrophy, as was evidenced microscopically by papilliferous projections into the acini. In thirty cases (41 per cent.) there was definite muscular atrophy, and in sixty-one cases (83 per cent.) the fibrous stroma was increased. In ten cases (13 per cent.) there was no evidence of associated hypertrophy in the sections examined from the glands, leaving 87 per cent. in which there was evidence of hyperplasia. Whether in these cases the hypertrophy was primary and the carcinoma implanted thereon, it was impossible to determine, though in many microscopic sections the apparent transition by almost imperceptible variations from simple hyperplasia to undoubted carcinoma was observed.

Usually one can be moderately certain of the cancerous nature of the tissue on gross inspection alone. When the operator's knife, in making capsular incision, cuts through tense tissue which does not bulge, the edges of which are firm and ridged, suspicion should be at once

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aroused. It has been our experience that carcinoma in no tissue, with a possible exception of small tumors of the breast, removed at the surgical clinic was more apt to escape diagnosis grossly than that of the prostate, so that it is our inevitable custom to make frozen sections from various areas of the removed gland and report to the surgeon while the operation is in progress.

Etiology: The etiology of carcinoma of the prostate is completely unknown as is that of carcinoma elsewhere. Albarran and Hallé insist on a definite relationship between prostatic hypertrophy and carcinoma. Among eighty-six hypertrophied prostates they found, in twelve, changes in the epithelium, which they thought to be different grades of carcinomatous degeneration. When one considers the difficulty of accurate diagnosis, however, especially in cases of carcinoma of the prostate, all such instances as the above must be regarded with some suspicion, unless all of the tissue of the prostate was removed at the original examination and a careful microscopic investigation made thereof.

While we may consider it fairly well established that isolated epithelium, whether from inherent or external stimuli, exhibits a tendency to proliferate and infiltrate, and while the observations of many workers record series of pictures such as those described by Albarran and Hallé, yet we must be conservative in our interpretation of these apparent transitional stages of hyperplasia into carcinoma. Likewise, we must examine most critically all clinical data, such as the observations of Prédal and others, suggesting the same line of development.

Metastases: Many prostatic carcinomas show a marked tendency to seize on neighboring structures, particularly the floor of the bladder, seminal vesicles and rectum. The lymph-glands in the region of the prostate are the first to become infiltrated with cancer. After that, the retroperineal and inguinal glands become involved. Metastases to distant organs are common, and should always be as carefully as possible excluded in clinical

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examination before operative procedure. They are frequently present in the lungs, liver, spinal column and long bones. Von Recklinghausen, Sasse, Brown, Kolisko, Frisch and others have emphasized the importance of seeking for small carcinomata in the prostate, breast or thyroid in cases in which extensive metastases in the bones have been found at autopsy. Von Recklinghausen says:

> **If, in the female, cancer of the vertebra breaks forth with unspeakable pain, as a rule, one does not err if he assumes the original focus to be in the breast. In such cases the primary focus may reach only to a very small size.**

Frisch says:

> **Perhaps just as frequently may the causative rôle for general carcinoma in man fall to the lot of prostatic cancer as to the lot of the breast-gland cancer in the female. We know how difficult it is to recognize prostatic cancer with the naked eye, how little it destroys the tissue, how very much more it tends to produce induration so that only the typical involvement of regional lymph-glands discovers and facilitates the diagnosis.**

As prostatic sarcomata develop they involve the bladder wall and neighboring structures. The neighboring lymph-glands are usually affected, but distant lymph-glands rarely. Metastases to other distant organs — lungs, liver, etc. — are also uncommon, though instances have been reported.

With regard to the histologic type of tumor, the round cell is the most common, and after this the spindle cell. Angio-, lympho-, myxo-, adeno-, enchondro-, leiomyo-, and rhabdomyosarcomatous forms have also been reported.

In concluding this incomplete review of an important subject, we trust, that, at least, our aim to stimulate keener interest in the study of the prostatic gland has been successful. It is a regrettable fact that many otherwise well-informed physicians seem to be almost unaware of the existence of this organ. At least they are prone to ignore its rôle in the production of a train of symptoms which they frequently ascribe to a "weak

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bladder" or "kidney disease." Often patients die of the sequelæ of prostatic hypertrophy, or directly from prostatic carcinoma, without ever having had a rectal examination. Patients have been operated on for chronic appendicitis when their symptoms were really due to carcinoma of an unexamined prostate. In every case of gonorrhea in the male the possible involvement of the prostate should be remembered and the patient warned, at the time, of the troubles probably in store for him in the future.

A rectal examination should be a routine procedure with all males presenting themselves for diagnosis of obscure abdominal as well as genito-urinary troubles.

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STUDIES IN INFARCTION

EXPERIMENTAL BLAND INFARCTION OF THE KIDNEY AND SPLEEN *

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The early history of the study of thrombosis and embolism is so completely reviewed in the articles of Virchow,[1] Cohn[2] and Welch,[3] that it seems hardly necessary at this time to consume time and space with its detailed presentation. It is very evident that Galen, Vesalius, Lancisi, Bartoletti, Bonetus, Boerhave, and Morgagni had, in a general way, fairly clear ideas as to the nature of these conditions, although, as would naturally be expected, they made no sharp distinctions between the two. Laennec's description of hemorrhagic infarction of the lung, under the name of pulmonary apoplexy, was most illuminating, although he seems to have had little knowledge of the nature of infarction in general. Rokitansky[4] had a much broader conception, but failed to differentiate the possible causes. The results of Cohn's experimental work, as well as of Pannum's,[5] are not conclusive, in that infection and sec-

* From the Department of Research Medicine and McManes Laboratory of Pathology, University of Pennsylvania. Aided by a grant from the Committee on Scientific Research of the American Medical Association.

1. Virchow, R.: Gesammelte Abhandlungen, Frankfort, 1856.
2. Cohn, B.: Klinik der embolischen Gefässkrankheiten, Berlin, 1860.
3. Welch, Wm. H.: Hemorrhagic Infarction, Tr. Ass. Am. Physicians, 1887, ii, 121.
4. Rokitansky: Handbuch der pathologischen Anatomie, Vienna, 1844, ii, 60.
5. Pannum, P. L.: Experimentelle Beiträge zur Lehre v. der Embolie, Arch. f. path. Anat. u. Phys., 1862, xxv, 308.

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ondary inflammatory changes were almost constant complications.

In 1872 Cohnheim[6] published his "Untersuchungen." The largest part of his work was done on the frog's tongue, but he also extended his experiments to the rabbit's ear, guinea-pig's mesentery and the mammalian kidney. He formulated the conception of end-arteries; a distinction which later observers, notably von Recklinghausen,[7] have shown to be less absolute than Cohnheim taught. Disregarding the earlier work of Cohn and of Blessig,[8] Cohnheim concluded from his own work that the blood in a hemorrhagic infarct represents a reflux from the veins.

Von Zielonko,[9] working under von Recklinghausen, studied areas of obstructed circulation in the web of the frog's foot. He showed conclusively that, at least in the web of the frog's foot, the blood enters and distends the capillaries of the infarcted areas from the capillaries of the neighboring areas and never by a return flow from the veins. He also showed that the arterial pressure in the surrounding areas is an important factor in determining the degree and rate of hemorrhagic extravasation. He noted at the end of five or six days the beginning decolorization of the hemorrhagic area. Kossuchin,[10] in 1876, working on the frog's tongue, reached practically the same conclusions; and in 1878 Küttner[11] demonstrated, by injections, the free capillary anastomosis existing between the bronchial and pulmonary circulations in both amphibian and mammalian lungs,

6. Cohnheim, J.: Untersuchungen über die embolischen Processe, Berlin, 1872.
7. Von Recklinghausen, F.: Handbuch der allgemeinen Pathologie des Kreislaufs, Stuttgart, 1883, p. 156.
8. Blessig: Ueber die Veränderung der Niere nach Unterbindung der Nierenarterie, Arch. f. path. Anat. u. Physiol., 1859, xvi, 120.
9. Von Zielonko, J.: Ueber Entstehung der Haemorrhagien nach Verschluss der Gefässe, Arch. f. path. Anat. u. Physiol., 1873, lvii, 436.
10. Kossuchin, A.: Zur Lehre von dem embolischen Infarkte, Arch. f. path. Anat. u. Physiol, 1876, lxvii, 449.
11. Küttner: Beitrag zu den Kreislaufsverhältnissen der Froschlunge, Arch. f. path. Anat. u. Physiol., 1874, lxi, 21; Beitrag zur Kentniss der Kreislaufsverhältnisse der Säugethierlunge, Arch. f. path. Anat. p. Physiol., 1878, lxxiii, 476.

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and thus opened the way for an explanation of the hemorrhagic character of pulmonary infarcts. A more effective influence, however, in overthrowing Cohnheim's teaching was Litten's[12] repetition, in 1881, of Cohn's and of Blessig's experiments on the kidney. After ligating the renal artery of the rabbit, he obtained greater hyperemia and hemorrhage when he ligated in addition the renal vein, than when he left it open; on the other hand, if he also ligated all sources of collateral circulation, the hyperemia and hemorrhage were reduced to a minimum even although he left the renal vein free. Von Recklinghausen[13] attributed to partial hyaline thrombi, which he observed in the capillaries of hemorrhagic infarcts of the lungs and spleen, an influence which raises the pressure in these capillaries and predisposes to diapedesis. Brown-Séquard[14] had pointed out the possibility that lesions of the vasomotor nerves accompanying the obstructed artery might be a factor in the capillary dilatation. Recently Bier[15] has emphasized the same possibility and has shown that, after section of the artery and vein of the hyperemic area, the blood still remains in the dilated capillaries; whence he concludes that the capillary dilatation is to some extent independent of the transmitted arterial or venous pressure. Mall[16] found it exceedingly difficult to inject from the mesenteric veins into the capillaries and impossible to inject from the veins back through the capillaries into the arteries.

Detailed studies of the anatomic and histologic changes in infarcts of the spleen and kidney, at different periods after infarction, have been made by several observers. Beckmann[17] believed that the infarcts of the

12. Litten, M.: Untersuchungen über haemorrhagischen Infarkte, etc., Ztschr. f. klin. Med., 1880, i, 131.
13. Von Recklinghausen: p. 160.
14. Brown-Séquard: Quoted by von Recklinghausen: See Note 7.
15. Bier, A.: Die Entstehung des collateralen Kreislaufes, Arch. f. path. Anat. u. Physiol., 1898, cliii, 434.
16. Mall, F.: A Study of Intestinal Contraction, Johns Hopkins Hosp. Rep., 1896, i, 37.
17. Beckmann, O.: Embolie der Arteria mesenterica superior, Arch. f. path. Anat. u. Physiol., 1858, xiii, 501.

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kidney were seen as pale infarcts with little evidence of blood, and opposed Rokitansky's view that the pale renal infarct represented a decolorization of the earlier hemorrhagic infarct. Later Weigert[18] emphasized the same conception of anemic infarcts as distinct from hemorrhagic infarcts, and in spite of much evidence to the contrary, his view attained wide general acceptance. Both von Recklinghausen and Thoma[19] apparently accepted his view. In 1877 Argutinsky[20] studied renal infarcts in the dog twenty-four hours and seven days after the injection of wax pellets into the aorta through the crural artery. Contemporaneously Uhthoff[21] made a similar study, using mercury instead of wax. Both observers noted the presence of hemorrhage, or of pigmentation the result of hemorrhage, widespread throughout the infarcted area, thus opposing the theory of Beckmann and Weigert. Talma[22] studied rabbits in which he ligated one branch of the renal artery. In the first twenty-four hours he found the infarcted area swollen and red, but laid stress on the hyperemia rather than on the hemorrhage. Foa[23] in a similar series found that a few seconds after ligation, the infarcted area might be pale, but that at the end of twenty-four hours it was swollen and red. He noted the presence of moderate hemorrhage.

In spite of this work, Thoma[19] in 1894, still described the renal infarct as pale from the outset. More recently Beattie and Dickson[24] report work done by Forbes[25] under Greenfield's direction, in which seeds were

18. Weigert, C.: Ueber die path. Gerinnungsvorgänge, Arch. f. path. Anat. u. Physiol., 1880, lxxix, 87; see p. 104.
19. Thoma, R.: Lehrbuch der pathologischen Anatomie, Stuttgart, 1894, vol. i.
20. Argutinsky, P.: Beiträge zur normalen und pathologischen Histologie der Niere, Halle, 1877.
21. Uhthoff, W.: Experimentelle Beiträge zur Nephritis, Inaug. Diss., Berlin, 1877.
22. Talma, S.: Der Verschluss der Nierenarterien u. seine Folgen, Ztschr. f. klin. Med., 1881, ii, 483.
23. Foa, P.: Ueber Niereninfarkte, Beit. zur path. Anat. u. Physiol., 1889, v, 275.
24. Beattie, J. M., and Dickson, W. E. C.: General Pathology, Philadelphia, 1908, p. 165.
25. Forbes, quoted by Beattie and Dickson: See Note 24.

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injected into the arterial circulation. In the kidney they note, in the early stages, congestion with slight hemorrhage, most marked in the medulla; later, pallor develops both centrally and peripherally, associated with necrosis throughout the infarct. In the spleen they find hemorrhage to be very conspicuous in the early stages, with decolorization appearing later.

Regarding regeneration in the kidney, Litten, Petrone,[26] Arnold,[27] Weigert, Podwyssozki,[28] Thorel[29] and Pearce[30] all have noted epithelial proliferation after various renal lesions, but no true tubule reproduction and no formation of new glomeruli. Pisenti[31] alone claims to have seen, after excising small pieces of kidney, some attempt at the formation of glomeruli and true tubules. Except in those cases associated with abscess formation, organization of the infarcted area has been noted by all observers, beginning, during the course of the first week after infarction, at the periphery and gradually extending toward the center. Very recently MacNider[32] has presented a series of experiments on the cat, in which he ligated one branch of the renal artery and made histologic studies at intervals of from twenty-two hours to ninety days, especial attention being given to the regenerative changes.

The present group of experiments represents the first of a series in which is contemplated the study of infarction in all its phases. Up to this time the greater number of investigators in the field have studied not only

26. Petrone, A.: La rigenerazione del fegato e del rene per neoformazione dei loro dutti escretori, Giornale Morgagni 1881, xxiii, 805.

27. Arnold, J.: Beiträge z. Anat. des miliaren Tuberkels, Ueber Nierentuberkulose, Arch. f. path. Anat. u. Physiol., 1881, lxxxiii, 289; see page 295.

28. Podwyssozki, Jr., W.: Ueber Regeneration der Drüsengewebe, Beitr. z. path. Anat. u. Physiol., 1888, ii, 3.

29. Thorel, C.: Ueber typische u. Pseudoregeneration bei Nierenintarkten, Arch. f. path. Anat. u. Physiol., 1896, cxlvi, 297.

30. Pearce, R. M.: Notes on Late Stages of Repair of Kidney Tissue, etc., Jour. Med. Res., 1909, xx, 53.

31. Pisenti: Sur la cicatrization des blessures du rein et sur la generation partielle de cet organe, Arch. ital. de biol., 1884, vi.

32. MacNider, William de B.: The Pathologic Changes which Develop in the Kidney as a Result of Occlusion by Ligation of One Branch of the Renal Artery, Jour. Med. Res., 1911, xxiv, 425.

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infarction, but also the closely related subjects of thrombosis and embolism. That these two latter conditions, of importance in the etiology of infarction, have distracted attention from the infarct itself is reflected in the insufficient reports on the gross and minute anatomy of infarcts and in the incompleteness of experimental procedures to elucidate the various changes found. We propose to study the anatomy of the infarcted areas in various stages, both under normal conditions of circulation and with certain experimental variations in the general circulation of the organ in question; we shall take up certain problems in physiology and physiologic chemistry suggested by our observations and shall extend the investigations to all the available organs of the body so as to be able, on the completion of the study, to make definite and conclusive deductions.

METHODS

The study presented at this time concerns infarction in the kidney and spleen of the dog under normal and variously altered conditions of circulation. In the spleen the vascular arrangement is comparatively simple and the only practicable experimental variation in circulation of any significance was the cutting off of the general arterial supply. In the kidney, however, the fact that the organ is supplied and drained by renal, ureteral and capsular vessels makes matters more complicated. With the capsular vessels we include the anastomoses with the adrenal and lumbar circulation. It was, therefore, necessary to study the kidney under the following conditions:

1. With normal circulation.
2. With renal artery ligated.
3. With renal vein ligated.
4. With renal artery and vein ligated.
5. With renal artery, vein and ureteral vessels ligated.

In female dogs the additional anastomosis with the ovarian circulation is usually very rich and required

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special ligation. In all cases with ligation of the ureteral vessels any possible flow of urine from the kidney was provided for by the insertion of a small aluminum cannula into the ureter, the silk being tied around it. Decapsulation in addition to universal ligation was not practiced, since it was found that it led to extensive suppuration of the kidney and, moreover, the universal necrosis under these conditions rendered the study of the infarcts impossible.

In ligating the splenic artery, particular care was taken to tie off also the branches anastomosing with the gastric artery. On several occasions simple ligation of the splenic veins was tried, but the early infarcts were entirely obliterated by the swelling resulting from this procedure, and the later ones showed no marked differences from those of normal spleens, with the exception that the entire mass of the spleen was much diminished and the organ pallid in appearance. Accordingly, it was felt that no additional information of value could be obtained from an extended series of this kind. The dogs in all the groups were killed two, four, twelve, twenty-four, forty-eight hours, and four and seven days after the production of the infarcts.

The operations were all done aseptically and under deep ether anesthesia. A median abdominal wound was made from 2 cm. above the umbilicus to the pubis and the left common iliac artery exposed. For the insertion of the emboli an annealed soft copper tube, 35 cm. long and 1 mm. in caliber, provided with a flexible steel obturator, was used. After orientation experiments with begonia, aldike clover, mustard and tobacco seeds, the last were found to be most satisfactory, and were used uniformly throughout the series. About 50 seeds were placed in the end of the copper tube in a space left by drawing the obturator back for a distance of 2 cm. The instrument was inserted into the iliac artery and as far up the aorta as desired. It was not long before sufficient skill was acquired to avoid abrasion of the intima of the

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aorta. For the production of splenic infarcts it was necessary to have the end of the tube 2 to 3 cm. above the origin of the celiac axis and to occlude, by pressure with the finger, the superior mesenteric, renal and right common iliac arteries. For the production of renal infarcts the end of the cannula was placed just below the origin of the celiac axis and the superior mesenteric and right common iliac arteries occluded. In those cases in which both renal arteries were left open, it was found that placing the cannula at any point above the origin of the right renal artery resulted in more frequent infarction of the right kidney than of its fellow; and when both organs were infarcted, the infarctions were more numerous in the right. For this reason most of the work was done on the right kidney. It was necessary to occlude the mesenteric artery temporarily, so as to avoid the entrance of seeds into the arteries of the intestines and the consequent production of gangrene. Where several renal vessels were ligated, the artery was tied first, then the vein, then the ureteral vessels, and, in females, the ovarian circulation.

Heavy white silk (Corticelli EE) was used for all ligations. The wound was closed by the usual surgical procedure, and after the given time had elapsed, the animals were killed with chloroform. At autopsy the success of the ligations was carefully determined, gross notes and diagrams were made, the tissues fixed in Zenker's fluid, embedded in paraffin and stained with Delafield's hematoxylin and alcoholic yellow eosin. The minute study of the slides was aided by and correlated with the gross diagrams and notes.

RESULTS

Grossly, the experimental infarcts of the kidney became distinctly visible at the surface of the organ in from three to five minutes after the injection of the seeds into the aorta. The first noticeable change was the appearance of a brilliant purple color which occupied a large part of the infarcted area. This congestion

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gradually extended until, in about ten minutes, the infarct in its entirety was sharply defined. (In only one infarct was there any exception to this rule. This was in a somewhat fibrosed organ, the infarct appearing first as a pallid area with a purple marginal zone, the entire area becoming purple, however, in less than two minutes after the infarct became distinguishable.) No definite swelling was noticeable in this early stage, probably because of the tension of the kidney capsule. At the expiration of two hours, however, the entire kidney, which at first had been of a bright pink color, became of a color so closely matching that of the infarct that the outline of the latter, in a large number of cases, was almost entirely lost. At the end of four hours, although still lacking in definition on the outer surface, the infarct could be fairly well defined in the cut surface. At this time in all the kidneys examined, the infarct was seen as a purple mass of deeper color than the surrounding kidney, rather poorly defined, moist and bloody, usually bulging on section and occasionally protruding somewhat above the surface of the organ. At this stage there was present in the vast majority of instances, a peripheral zone rarely more than 1 mm. in width, in which the tissue was somewhat lighter in color than in either the infarct or the surrounding kidney substance. The fact that this zone could not be distinguished microscopically, leads to the conclusion that it represents a zone of relative compression anemia. This pallid area remained visible for several hours, disappearing in from twenty-four to forty-eight hours, when the infarct reached the limit of its elevation and deep color and began to fade and retract. Necrosis began in the infarcts of the normal kidneys in forty-eight hours, the same being true of the infarcts in those kidneys in which the arterial supply was cut off without other interference with the circulation. After simple ligation of the vein, necrosis appeared in the infarct at the end of twenty-four hours; and with additional liga-

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tion of artery and ureter, it appeared in from twelve to twenty-four hours. Usually coincident with the necrosis, a clearly visible, but always very narrow, zone of reactive hyperemia appeared at the margin of the infarct, but congestion of this kind was by no means a constant feature. The necrosis appeared first as irregularly distributed, minute areas near the middle of the infarct, in the later stages becoming larger and fusing to form solid, fairly large masses of necrotic material. In the late infarcts (four to seven days old) where the outer surface and cut surface showed retraction of the infarcted mass, the central necrotic mass was often surrounded by a red zone, which histologically was found to be in part the remnant of suffused blood that had not undergone complete necrosis and in part blood which had infiltrated from the reactive hyperemia. Outside this zone was frequently seen a pallid zone which histologically corresponded to the zone of forming connective tissue. There is little doubt that with the progress of the necrosis, the intermediate zone of redness gradually disappears. Furthermore, in small infarcts this red zone was completely absent at the end of seven days. It must be said, however, that the sequence of gradual changes was not shown nearly so well in gross as in microscopic specimens. Indeed, it seems highly probable that the infrequence of the finding of red infarcts in the human kidney, is due to the fact that in this early stage the infarcted area is so ill defined as to be practically indistinguishable. A point of considerable interest is the fact that the infarcts were often very irregular in outline and varied markedly in general conformation, being most frequently conical, but very frequently hemispheric or cylindric.

The infarcts of the spleen became easily visible even more rapidly than did those of the kidney. They appeared as deep purple, fairly well-defined areas, usually triangular in shape near the poles or margins, but when occurring midway between the poles, extending as linear

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masses transversely across the organ. No portion of the spleen was more commonly infarcted than another. The most striking feature of the infarcts in this early stage is their marked swelling, which in many cases caused infarcts 1 cm. broad to project 3 to 4 mm. above the surface of the organ. At two and at four hours after infarction, the appearance of elevation was lessened and the outline of the infarct was not so well defined, probably because of the general enlargement and increased depth of color of the organ resulting from general congestion. A small percentage of the earlier infarcts showed a narrow pallid marginal zone, similar to that sometimes seen in the kidney infarcts, but again histologic examination failed to prove its nature. Necrosis did not appear in the infarcts of the spleens with unaltered general circulation until a week had elapsed, but in the series in which the splenic artery was ligated, necrosis was noted at the end of forty-eight hours. The necrosis, at first, was irregularly distributed, but later extended throughout the center of the infarct, except in one infarct in which the white necrotic mass had a central dry, red area. No zone of reactionary hyperemia was demonstrable at any stage of the condition, and it may safely be said that the only significant difference brought about in the course of the infarcts by artificially altering the circulation was that ligation of the artery caused necrosis to appear earlier than when the general circulation was not disturbed.

Histologically the infarcts presented pictures that showed very clearly the progress of the condition. In those infarcts which grossly were distinguished only with the greatest difficulty, the microscope showed unmistakable signs of focal interference with circulation and no mistake in the diagnosis was possible. Rather vaguely outlined in the early stages, definition became clearer and sharper as the condition progressed.

In the normal kidney, two hours after infarction, there was a small zone of subcapsular hemorrhage over-

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lying the infarct, and well-marked congestion of the intertubular capillaries and of the capillaries of the tufts. The blood in both regions was distinctly conglutinated, although in a specimen taken one hour after infarction (not included in the general series and only differing in this one respect) the conglutination had appeared in the intertubular capillaries, but not in the glomerular loops. The blood at this time was confined to the vessels, with the exception of a few corpuscles found here and there in the midst of the space occupied by a very well-marked interstitial edema, and in the subcapsular space which also showed a finely granular albuminous deposit, evidently of an edematous fluid. The tubular epithelium, especially of the convoluted tubules, showed marked cloudy swelling but practically no desquamation, and the nuclei of these cells showed slight fading of the central chromatin, the margins being still sharply defined. The lumina of the tubules were somewhat enlarged because of thinning of the cells surrounding them, but were well filled with a finely granular albuminous material, probably edematous in character. The larger vessels and the vessels of the medulla showed fairly well-marked congestion, but the medulla in this, as well as in all other sections, showed no other notable changes except for moderate fibrosis in the very late stages.

At four hours the conglutination had progressed, and some of the blood in the middle of the infarct showed fading of the hemoglobin. The tubular epithelium was more markedly degenerated and showed moderate desquamation. Desquamation and well-marked cloudy swelling were also observed in the epithelium lining the capsule of Bowman. The edema had become more marked in all situations, being accompanied in the glomerulus by distention of the capsule. Well-marked pyknosis and karyolysis were present.

At twelve hours, aside from the fact that the infarct was sharply defined, there were no notable changes except in degree.

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At twenty-four hours the infarct was very clearly defined and it had become possible to distinguish two zones: an outer zone in which the necrosis had evidently come on rapidly, giving the infarct its sharp definition; and an inner zone where hemorrhage had become well marked. The tubules and subcapsular spaces of this marginal zone appeared as coarsely granular, or almost hyaline, acidophilic masses and the interstices between the tubules, in the inner part of this zone, were occupied by conglutinated red blood-cells, and, in the outer part, by fresh, well-stained, non-conglutinated red cells, the latter being largely intravascular and very evidently dependent on a slight hyperemia in the surrounding living tissue. A few polymorphonuclear leukocytes were found in this zone.

At forty-eight hours the conditions were much the same, except that the center of the infarct showed hemorrhage more clearly, and the fading of the red cells had progressed to a considerable degree.

At four days the necrotic central zone was greatly increased in size. A zone of solid necrosis, seen as a peripheral zone in the preceding sections, now became an intermediate zone, due to the appearance of an outer marginal zone of growing connective tissue, somewhat poorly vascularized. No mitotic figures were demonstrable.

At seven days the fibrosis was more extensive, and occasional mitotic figures were seen in the tubules near the margin, but with no evidence of new formation of tubules.

Ligation of the renal vein resulted in several changes in the microscopic appearances of the infarcted and non-infarcted areas. The most notable change was in the blood content, which in the infarct was very much greater than in the non-infarcted area; and two hours after infarction there was seen slight, but easily demonstrable, hemorrhage into the subcapsular space and the interstitial tissue of the pulp. Edema was about the

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same in this as in the preceding series. The infarct became sharply defined in four hours (earlier than in the first series), showed somewhat more rapidly progressing hemorrhage and conglutination and an early fading of the masses of blood in the middle of the infarct which became almost complete at twenty-four hours. As a whole, the series was characterized by more marked circulatory alterations and more rapid degenerative changes in the parenchyma than were evident in the kidneys with normal general circulation. At four and seven days after infarction, the central zone showed a rich, very fine network of fibrin in the positions from which the erythrocytes had disappeared. The new growth of connective tissue was not especially different in progress or character from that seen in the previous series. In the surrounding kidney substance, cloudy swelling, edema, and congestion were observed very early; definite necrosis was not demonstrated; hyaline casts became evident in four hours, and rapidly increased; and regenerative changes in the epithelium were not demonstrable.

With ligation of the renal artery alone, the blood conditions in the infarct were much the same as in the series with normal general circulation, except that the blood-content of the necrosing area was less, although not markedly so. The changes in the suffused blood progressed with the same rapidity as in the first series; the infarct became sharply defined at four hours (earlier than in the first series, at the same time as in the second series); decolorization of the corpuscles was well-marked at twelve hours and progressed somewhat more rapidly than in the first, and less rapidly than in the second, series; degenerative changes in the parenchyma followed much the same course as in the second series, and fibrin appeared in the center of the infarct just as in the second series. Organization was well-marked at four days. A few mitotic figures were found in the epithelium immediately surrounding the infarct at seven days. The

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non-infarcted areas showed, in the early stages, well-marked capillary congestion which became much less marked after twelve hours; also moderate edema, well-marked cloudy swelling, going on to distinct necrosis in the later stages, and in the seven-day kidney the presence of hyaline casts.

On ligation of the renal vein in addition to ligation of the renal artery, the infarcts progressed in practically the same way as with ligation simply of the renal artery. This statement applies to blood-content, blood-changes, degenerative changes, and regenerative appearances. Neither did the appearance of the non-infarcted areas differ in any essential feature.

Ligation of renal artery, renal vein and ureteral vessels (and, in female dogs, the ovarian anastomoses) resulted in no distinct variation in the amount of blood in the infarct, or in the subsequent alterations in the blood, from that seen in the third and fourth series, and organization was not noticeably retarded, but the infarct became sharply defined histologically at the end of two hours (more rapidly than in any of the other groups), necrosis progressed with great rapidity (also clearly noted grossly at twelve to twenty-four hours) and no mitotic figures were found in the surrounding epithelium. The non-infarcted kidney substance was anemic from the first and showed rapidly progressing degeneration and necrosis of the epithelium. Hyaline casts were present in considerable numbers at, and after, twenty-four hours; only in the series in which the renal vein alone was ligated, had they been seen so early and in such great numbers.

Throughout all the groups careful microscopic examination showed no very marked leukocytic infiltration. The slight degree of infiltration noted was always marginal, never showed deep penetration and usually appeared at from twenty-four to forty-eight hours.

The spleen at the end of two hours showed rather poor definition of the infarct histologically, with a narrow

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zone of uninfarcted tissue immediately under the capsule. In the periphery of the infarct was found a marked distention of isolated blood-sinuses with but little or no extravasation. The pulp in this area showed no change, but in many instances the follicles, even though not apparently within the zone of infarction, showed slight pyknosis and karyorrhexis in those cells situated near the middle of the follicles, but not in direct apposition to the central artery. In the middle of the infarct there was more marked distention of the sinuses, more uniformly distributed congestion and very distinct extravasation. Here, also, the follicles were uninvolved by the hemorrhage, but showed somewhat more marked pyknosis and karyorrhexis than did the follicles at the margin of the infarct. Those parts of the pulp that were almost obliterated by congestion and hemorrhage showed moderate pyknosis and karyorrhexis in the remaining cells. Conglutination was moderate in the areas both of congestion and of hemorrhage. The non-infarcted areas showed no pathologic alterations.

At four hours the only changes worthy of note were somewhat more marked conglutination, more extensive nuclear degeneration and a degeneration of the protoplasm of the cells in the infarcted zone as shown by a lessened affinity for the eosin. Trabeculæ, blood-vessel walls and follicular outlines were well preserved.

At twelve hours the infarct became sharply defined by the extension of the hemorrhage into the marginal zone, which previously had shown only congestion. Conglutination was well-marked and necrosis advanced. In the pulp immediately surrounding the infarct, there was a moderately well-marked infiltration of leukocytes which, however, penetrated but a very short distance into the hemorrhagic area.

At twenty-four hours no additional changes could be demonstrated.

At forty-eight hours conglutination had reached such an extreme degree that the infarct appeared as an almost

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hyaline, red mass, containing the trabeculæ and small circular areas of nuclear fragments representing the follicles. At this stage the nuclei of the trabeculæ showed a marked diminution in the affinity for the hematoxylin. The marginal leukocytic infiltration was about the same as at twenty-four hours.

At four days the infarct was sharply defined and still showed a narrow zone of living tissue immediately beneath the capsule. In the margins of the infarct a few of the trabeculæ with their blood-vessels persisted apparently uninjured. From the tissue immediately surrounding the infarct, i. e., from the trabeculæ in the margin and their blood-vessels, from the fine fibrillar connective tissue framework of the living pulp, from the thin layer of living tissue underlying the capsule and from the capsule itself, a slight new growth of connective tissue, rather poorly vascularized, had developed. The infarct itself appeared as a mass of almost completely decolorized erythrocytes and many irregularly distributed nuclear fragments. In the center of this mass, the red blood-cells had almost completely disappeared and there was found a fine network of fibrin, enmeshing a relatively small number of fine albuminous granules.

At the expiration of one week, the new growth of connective tissue was somewhat more extensive; the leukocytic infiltration had almost completely disappeared, and the central area of complete necrosis and fibrin formation was somewhat more extensive. At this stage was present a very slight hyperemia in the smaller vessels outside the zone of organization, a feature not demonstrable earlier in the course of the development of the infarct. At no time could granular or crystalline pigmentation of the infarct be demonstrated.

Ligation of the splenic artery produced practically no change in the microscopic character of the infarct, except that the process extended to the capsule without any intervening rim of living cells. In the later infarcts,

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however, a zone of new growing connective tissue appeared between infarct and capsule, evidently taking its origin from the latter structure. Decolorization of the erythrocytes appeared somewhat sooner than in the preceding series and progressed more rapidly. Necrosis of the cells of the pulp and follicles followed the same course as in the spleens with normal general circulation. The non-infarcted tissue showed no effect of the ligation, except that, after one week, the protoplasm of the larger lymphocytes and endothelial cells showed diminution in affinity for eosin.

CONSIDERATION OF THE DATA

In the discussion of the various facts established by, and inferences to be drawn from, this study, it is proposed to take up, first the circulatory changes with especial reference to congestion, conglutination of red blood-cells, solution of hemoglobin, fibrin formation, then the progress of degenerative changes in parenchymatous and connective tissues, and finally the evidences of regeneration and organization.

A conclusion from the work that is unavoidable is that, in the kidney and spleen, all infarcts are primarily hyperemic. The term "hyperemic" is used advisedly, for in the earlier stages, at least in the kidney, hemorrhage plays a very unimportant part in comparison with hyperemia. In the spleen, the extravasation can be seen distinctly in the center of the infarct four hours after embolism, but in the kidney it does not become an important feature for from twenty-four to forty-eight hours. The hyperemia is diffuse and is much more striking in the capillaries and small vessels than in the larger arteries and veins. The hemorrhage is considered by most writers to be the result of diapedesis due to injury of the vessel walls. From our histologic examination this statement cannot be gainsaid; indeed there is much experimental evidence for accepting it. In the walls of the larger arteries, however, we were not able conclusively to demonstrate early degeneration; their

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walls were distinctive until long after the hemorrhage had appeared. This does not by any means controvert the statement in question, because diapedesis naturally would take place from the smaller vessels, vessels whose walls are not likely to be well defined under conditions such as are found in the infarcted areas. In the kidney, the early hyperemia was most notable in the intertubular and glomerular capillaries, and as it was in these places that extravasations were seen there is little room for doubt that the capillaries which are the seat of the most intense congestion, furnish the blood that later appears as extravasations. In the spleen, the sinuses of the pulp showed intense early congestion, a congestion which was not, and did not later become, evident in the follicles; the hemorrhage appeared in corresponding position and evidently came from the thin-walled vessels.

In determining the source of the congestion, arteries, veins and capillaries must be considered. It is very unlikely that the capillaries play an important part, because very early they become occluded with the conglutination thrombi, which will be discussed later. In addition, the work of Mall[16] leaves very little doubt that physiologically the capillaries soon become impermeable. The possibility that reflux from the veins plays an important part has also been ably refuted by the same writer. In addition also, the study of our specimens shows that ligation of the veins had practically no effect in varying the amount of congestion after the pressure of the arteries had been eliminated. That the general vascular pressure in the kidney has an influence on the blood-content of the infarct, was shown by the increased amount of blood in the infarct when the vein alone was ligated. Ligation of the main artery and vein was followed by the appearance of relatively little blood in the infarct, doubtless because of the relatively low pressure maintained by the collateral circulation. Cutting down the circulation to a minimum, however, as was done by additional ligation of the ureteral and ovarian circula-

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tion, was in no case followed by what might be called an anemic infarct. Where all circulation was cut off, necrosis was so extensive that no infarcted areas could be clearly seen. The assumption is obvious, therefore, that whatever hyperemia is present, is due to the dilatation of the vessels in the infarcted areas and is dependent on the arterial pressure of the surrounding, living tissue; regurgitation from the veins plays no significant part in its production.

Edema of the interstitial tissues and the presence of an excess of albuminous precipitate in the subcapsular space, were constant and early but tended soon to disappear.

Marginal hyperemia, the so-called collateral hyperemia, usually did not appear until forty-eight hours or more had elapsed. It would seem that this is a local condition dependent on the irritation of the necrotic mass, because it did not appear until necrosis was distinctly in evidence. That it is local was evidenced by the fact that variations in general circulatory conditions did not appreciably influence it.

The term conglutination, used freely in describing the microscopic appearance of the infarcts, is taken to mean clumping and fusion of the corpuscles; mere clumping, however, is of little significance because, of necessity, the corpuscles are in close apposition as they lie in the tissues and vessels. The condition appeared within two hours after infarction, gradually became more marked and reached its height in from twenty-four to forty-eight hours, and then slowly became less manifest because of fading of the corpuscles. Little change in this process was found under the various circulatory conditions, except that in the series of kidneys in which the vein alone was ligated, conglutination reached its height somewhat earlier than in the other groups. What part the heightened pressure played in this variation is problematic, but it seems likely that the chief reason why the change was so notable is that, when the vein alone

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was ligated, the vessels were richer in blood and the extent of conglutination correspondingly great. In the spleen, conglutination occurred much as it did in the kidney, the only difference being that it appeared to be fairly extensive in the earlier infarcts, probably because the blood is in greater masses in the distended splenic sinuses than in the smaller kidney capillaries.

Fading of the corpuscles or solution of their hemoglobin did not appear, as a rule, until forty-eight hours had elapsed. It was usually seen in the center of the infarcted mass and progressed peripherally, but even at the end of a week, at least in the larger infarcts, there was usually a fairly large mass of conglutinated, well-stained cells between the central pale areas and the marginal zone of the infarct. In none of the slides was granular pigment deposit found, and it seems probable that the hemoglobin diffused into the surrounding tissues without further decomposition. If any flow of tissue juice or plasma occurs in the vessels of the infarcted area it must be extremely slight because of the conglutination thrombi in the capillaries and the coagula in the larger blood-vessels. It is but natural to expect that the earliest and most extreme degeneration would occur centrally, because this part of the mass is furthest from the source of nutrition. It is not likely that leukocytes play any part in the removal of the hemoglobin, because none of the specimens showed deep penetration of these cells into the infarct. Indeed, with the exception of some of the later infarcts in the spleen, there was never more than a very moderate peripheral infiltration of polymorphonuclears, and in the kidney the lymphocytes were even less prominent. That venous drainage has little or nothing to do with the decolorization, is evidenced by the fact that ligation of the vein played no important part in the fading of the cells, the central pallor of the infarct appearing quite as soon in this series as in the others. The same is true of changes in the arterial conditions, for solution of the hemoglobin

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was quite as prominent a feature in the groups in which the artery was tied as in the group in which no vessels were ligated. It would appear, therefore, that plasmatic diffusion is responsible for the disappearance of this pigment.

Coincident with the disappearance of the hemoglobin, fibrin could be seen in the center of the infarcted area. It did not appear as heavy bands at any time, but was clearly distinguishable as a closely woven mesh of very fine threads with the typical nodes at the points of intersection. This applies equally well to kidney and spleen.

The degenerative changes in the parenchyma put in their appearance early, first as simple cloudy swelling, then desquamation, nuclear degeneration and finally at the end of about forty-eight hours, complete necrosis. All these changes reached their height in the central parts of the infarct before the marginal parts became affected, and also showed more markedly in the convoluted than in the other tubules. An interesting feature is the fact that the epithelium in the center of the infarct tended to break up into a finely granular mass, whereas that in the margin, slightly affected at first, suddenly underwent complete necrosis and the necrotic material filled the tubular spaces as a coarsely granular, almost hyaline mass. This marginal epithelium probably receives just sufficient nutrition by imbibition to keep it alive for a short time. When this nutrition fails, probably because of the pressure of the swelling infarct, the epithelium suddenly undergoes this peculiarly rapid necrosis.

In many of the infarcts, for the first twenty-four or forty-eight hours, a small number of tubules in the margin and, indeed, a few fairly deep in the infarct, retained their form and normal staining reactions, but at the end of this time, as the infarct became sharply defined, these tubules became less frequent and were very exceptional in older infarcts.

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In the spleen, the degeneration of the cells of the pulp and follicles appeared first as nuclear pyknosis and fragmentation, which was especially evident in the center of the follicles. It extended rapidly, however, so as to involve the entire follicle and pulp. The protoplasm showed little demonstrable change until about forty-eight hours had elapsed, when there was distinct solution.

The interstitial tissue did not degenerate until late in the course of the condition. In the glomerular tufts necrosis was evident first in nuclear fragmentation and then in complete disappearance of nuclei and vascular loops. In the spleen, the trabeculæ lost their nuclei rather by lysis than by rhexis, and subsequently the whole mass of tissue lost its outlines.

Regeneration of the parenchyma in the kidney was evidenced only by the presence of mitotic figures, sometimes typical and sometimes atypical, in the tubules immediately surrounding the infarcted zone. In concordance with other workers, we were unable to demonstrate tubule formation. We were not able to demonstrate regenerative changes until a week had elapsed, and in the series in which artery, vein and ureteral circulation were cut off, the sections showed no mitoses whatever.

In the spleen, no evidence of regeneration was found. In both spleen and kidney, however, organization at the periphery of the infarcted areas was demonstrable at four days and was well under way at the end of one week. The newly-formed tissue in both organs was notably poor in new blood-vessels. In the kidney, variations in the growing connective tissue, under the differing circulatory conditions, was not noted.

In the series in which practically all the circulation was cut off, marked progressing fibrosis throughout the non-infarcted areas was present, but the growth immediately about the infarct was no greater than in the other series.

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CONCLUSIONS

The most important conclusions are:

1. Regardless of general circulatory conditions, all infarcts of the kidney and spleen of the dog are first hyperemic, then hemorrhagic and finally become pale from coagulation necrosis.

2. The hyperemia of the early infarcts is, in a general way, proportional to the vascular pressure within the organ as a whole, and is not due to reflux of blood from the veins.

3. Conglutination of the red blood-corpuscles is the earliest demonstrable change in the blood of the infarct; removal of pigment from the infarcted area is probably due to plasmatic diffusion; definite fibrin formation appears relatively late in the course of the condition.

4. Necrosis progresses more rapidly in infarcts in those organs in which the general circulation is altered in some way (either from damming back of blood by vein ligation, or from cutting down arterial supply), than in organs in which the general circulation is normal.

5. The pallor of the white infarcts is due to decolorization of the contained conglutinated and coagulated blood; decolorization begins in a general way in the middle of the infarct and extends peripherally.

6. Organization progresses as well in organs in which the general circulation is diminished as in those in which the general circulation is normal.

7. Regeneration is seen, in the kidney, only in the occurrence of mitotic figures in the epithelium near the margin of the infarct; it is diminished by any decrease in the general circulation. Regeneration of the cells of the splenic pulp or follicles is not demonstrable previous to, or at the end of, one week.

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THE INFLUENCE OF THE THYROID AND PARATHYROID GLANDS ON THE HEALING OF FRACTURES *

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Since skeletal disturbances are so striking a feature in athyreosis, it is easy to conceive that a fractured bone in an animal deprived of thyroid gland would suffer delay in healing. That this is true seemed to be proved by Steinlen in 1900, who, using young rabbits, observed a definite delay in the time of fracture healing in animal operated on. The same was explained as a result of the delay in callus formation and lack of calcium deposit, so that there was a persistence of uncalcified cartilage beyond the period when normal animals showed unmovable solid bone.

While the results of Steinlen seemed conclusive, they were attacked by Pezzolini (1903) who asserted that it was not the thyroid removal, but the general cachexia of the animal that retarded healing and regeneration.

Still more recently (1909) Canal, and also Morel, basing their assumptions on the theory of the relation of the parathyroid glands to calcium metabolism, found that fractures healed more slowly after complete parathyroid removal than in control animals. Jovane and Vaglio, however, dispute their results.

In our experiments we have attempted to observe the results of both thyroid and parathyroid removal on the time of fracture healing as well as a few attempts at the production of thyroid hypertrophy during the course

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of fracture healing. This work we consider incomplete, for, although over fifty dogs were used, so many factors enter into the cause of delay in fracture healing that much more work must be done before any definite conclusion can be drawn. Among the points to be considered are age, size and individual susceptibility in the different animals. Considerable variation (even to absolute lack of union) can be obtained by variations of the technic with which fractures are performed. It is needless to say, also, that slight inexactness in the apposition of the fractured fragments may give considerable differences in the size of the callus, and that the animal must be carefully watched throughout the whole course of the recovery to prevent injuries that might retard healing.

Aside from all this, the greatest difficulty which we encountered in this work was the complete removal of all thyroid tissue. Anyone who has worked with dogs knows how infrequently myxedema symptoms occur in these animals, even when all visible thyroid tissue is removed. We were able to account for this by the finding of pericardial thyroid tissue in 80 per cent. of our animals, as we have described elsewhere.

Taking all these varying factors into account, then, we give the following results of our work. The malar bone was selected in most instances for fracture. In some cases the femur was fractured. Most of the experiments were following complete thyroidectomy. One series was following mass ligation of the parathyroid glandules, since it has been shown that these organs may be gradually destroyed in this way without the sudden tetanic death which follows complete parathyroidectomy.

After the removal of all visible thyroid tissue and the attempt to leave behind at least two parathyroid glandules to prevent tetany, the animal was left for from two to eight months and watched for the development of signs of myxedema. Out of twenty-one animals thus operated on, only two developed distinct myxedema, as was shown by the increase in size, the thickening of the

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skin and subcutaneous tissue, and the falling out of hair. (Several animals in this series died from sepsis and tetania parathyropriva.)

By experiments on control animals, it was found that healing of the malar bone, when chiseled through and the fragments carefully approximated and covered with periosteum, showed practically complete healing in about forty days. While a number of animals were examined at shorter and longer intervals, it was decided to use the myxedematous animals for study of the bone thirty days after the fracture. Several of the thyroidectomized animals not showing myxedema were also examined thirty days after fracture, and normal animals with thirty-day-fractured malar also were used for control.

While differences were found in the amount of union that had taken place, these differences were greatest between different animals in the control series and not between the control animals and the thyroidectomized animals. For instance, there were two cases of lack of union and both were in control animals. In general, in the control animals and in the thyroidectomized animals, both with and without myxedema, practically identical pictures were obtained.

Macroscopically, the fractures were well united with little or no visible callus. When the bone was removed, fibrous union could be seen, and the section showed fibrous tissue between the bone fragments.

Microscopically, considerable difference is to be noted in individual animals in the amount of connective tissue between the bone fragments. This may vary from a hardly discernible line to the width of two-thirds of a low-power microscopic field. When the bone is fixed in Zenker's fluid and stained with Mallory's anilin-blue connective tissue stain, the calcium content of the bone usually takes a distinct brown (or brownish yellow) color. With this stain, no lack of ossification is to be observed in the thyroidectomized animals that is not shown in the control animals.

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Following the negative results obtained in this series of experiments, a method was sought whereby the influence of the parathyroid glandules on the healing of fractures might, in some measure, be ascertained. Canal states:

> In my experiments on animals completely parathyroidectomized, I have observed that there is a delay in the healing of the fracture when compared with the animal of control under the identical condition of feeding and living. However, in experiments on animals partly parathyroidectomized, I have found that there is not the least delay in the healing.

While we do not know how Canal's results were obtained, one of us has shown in a previous article that dogs may be kept alive for some time even after complete destruction of the parathyroids if this is brought about by gradual destruction of the glands by mass ligation. The animal finally dies, but from cachexia instead of tetany, sometimes remaining in a state of torpor for several weeks.

Our experiments were carried out on only six animals in this series. The femur was the bone selected for fracture. Control animals show complete repair in one month after fracture of this bone. No comparative results that we care to record were obtained with the animals operated on. The extreme cachexia which these animals suffer, when successful operative results are obtained, makes comparison with normal animals impossible.

In conclusion, we find that, in the limited amount of material which we have studied, the lack of thyroid tissue has no influence on the healing of fractures of the malar bone of the dog. We see at present no exact method of studying the results of complete parathyroid removal on the healing of fractures.

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THE PATHOGENESIS OF CARDIAC HYPERTROPHY AND MYOCARDITIS *

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In several former papers[1] we described a simple method which permitted us with great certainty to produce a combination of hypertrophic and myocarditic changes within a relatively short time in the heart of the rabbit. At the same time we suggested an explanation of these phenomena without, however, going into any detailed discussion regarding the basis for our theoretical conceptions. Inasmuch as it appears to us that the principle underlying our explanation of the phenomena observed in the rabbit may, perhaps, be extended to the pathology of the heart in man, we believe that a somewhat more detailed discussion of our theory might be of advantage.

The method employed by us in the production of hypertrophic and myocarditic changes in the heart of rabbits was, briefly, as follows: We injected into the ear-vein of a rabbit a single small dose of epinephrin (0.2 c.c.) preceded by spartein sulphate or caffein sodium benzoate. We found macroscopic changes in the heart muscle a few days after the injection, which, however, were most marked ten to fourteen days after the injection. Shortly after the injection slight interstitial edema was found in the heart, and somewhat later the muscle fibers showed slight increase in size. Several days after the injection, the muscle fibers were distinctly

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1. Fleisher and Loeb: Arch. Int. Med., February, 1909; 1910 vi, 427; Centralbl. f. Path., 1909, xx, 104; THE JOURNAL A. M. A. 1909, liii, 1561.

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increased in size and their nuclei were also larger; the connective tissue between the muscle fibers was increased in quantity.

In the next few days the changes became more pronounced. The separation of the muscle fibers due to edema was now marked. In places we found degenerative changes in the muscle fibers; some of the fibers appeared to have been dissolved, only a thin ring of muscle substance surrounding the nucleus; the striations were now indistinct in the fibers.

About two weeks after the injection the changes had reached their maximum. The connective tissue increase was diffuse. The degenerative changes in the muscle proper had become more extensive. Besides a larger number of the muscle fibers and their nuclei were increased in size, and frequently double nuclei were seen in the muscle cells.

From this period onward the changes became less marked, both macroscopically and microscopically. The hypertrophy of the muscle fibers and muscle nuclei gradually disappeared; the degenerative changes were no longer apparent. Finally, twenty weeks after the injection, small islands of fibrous tissue which had supplanted the degenerated muscle fibers were the only remaining evidences of the hypertrophy of the heart and myocarditis.

The explanation which we offered was based on certain experiments carried out on striated muscle by several investigators.

Ranke,[2] who studied the influence of tetanic contraction on muscles, found that muscles tetanized by either strychnin or a galvanic current showed an increased content of water. This larger percentage of water he considered to be due to increased imbibition and decreased resistance to the passage of water into the muscle. This change in the water content of the muscle was supposed to be due to an increase in dissociated

2. Ranke: Tetanus, Leipsic, 1865.

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products within the cells caused by the activity of the muscle.

Cooke[3] later found that in tetanized muscles, in muscles fatigued by carrying a load, or even muscles which had been exposed to a single electric shock, the osmotic pressure was increased, such muscles taking up water from a solution hypertonic to normal resting muscles. This author further showed that this increase in osmotic pressure was not due to the electric stimulation as such, nor was the taking up of water due to the stretching of the interstitial spaces.

Fletcher[4] obtained results which, in the main, were similar to those of Cooke. He found that fatigue increased the osmotic pressure of muscles, but his findings differed from those of Cooke, as far as the subsequent curve representing the movement of water into the muscle and the influence of various strengths of solutions on the rate at which fluid was taken up were concerned.

In regard to the principal fact, namely, the taking up of water by fatigued muscles, and in regard to the increased osmotic pressure of fatigued muscles, the three authors mentioned were in agreement. On the basis of these facts and other observations which had proved that the growth of plant cells depends on an increase in turgor, and that also the growth of cells in lower animals depends on an increased taking up of water, J. Loeb[5] explained the hypertrophy of muscles resulting from increased work as due to the taking up of water following catabolic processes in the muscle leading to an increase in osmotic pressure. He also suggested that hypertrophy under pathologic conditions, in which no increased activity had preceded the hypertrophy, might be explained in a similar manner.

We assumed that as a result of the excessive work done by the heart muscle following the injection, the

3. Cooke: Jour. Physiol, 1898, xxiii, 137.
4. Fletcher: Jour. Physiol., 1904, xxx, 414.
5. Loeb, J.: Arch. f. d. ges. Physiol., 1894, 106, 270.

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osmotic pressure of the muscle and consequently the movement of water into the muscle fibers was increased. After the period immediately following the injection, the conditions in the experiments performed with striated muscles *in vitro* differ from the conditions prevailing in our experiment. In the former case, the muscle was kept *in vitro* under abnormal conditions and the fatigued muscle no longer performed any work. In our experiments the muscle remained in the body, was perfused with normal blood and continued to perform work. These differences might explain the further changes found in our experiments.

We must assume that the continued work of a muscle that has taken up an abnormal amount of water may lead to further taking up of water and to processes of vacuolization and solution in some muscle fibers. This excessive effect may, therefore, lead to degenerative changes. The primary interstitial edema and perhaps the stretching of connective tissue fibers may lead to the early increase of interstitial tissue, which we found—the later increase in connective tissue being secondary to the parenchymatous changes in the muscle fibers. The increase in connective tissue and consequent shrinking of the fibrous tissue causes pressure on the muscle fibers and may thus lead to secondary parenchymatous changes in the latter.

Before we proceed further, let us consider in what other way it might be possible to explain the facts observed by us experimentally. First, it might be assumed that epinephrin causes changes in the heart, not through its action on the heart muscle, but by causing a contraction of the coronary vessels, thus indirectly interfering with the nourishment of the myocardium. Some facts might be cited in favor of such an interpretation. In the first place, it is well known that epinephrin causes a constriction of small arteries. It is also an established fact that a partial or complete occlusion of the coronary vessels produces degenerative and fibrous changes in the

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heart muscle. Plausible as this explanation may appear, it does not seem to us to be tenable. In the first place, the experimental evidence points very strongly to the conclusion that epinephrin does not cause a constriction of the coronary vessels.

Schaefer,[6] who studied the outflow of blood from the coronaries, was unable to demonstrate any influence of epinephrin on these vessels. Langendorff[7] found that this drug caused dilatation of cut-out strips of the coronary vessels of sheep and his results were confirmed by Pal;[8] DeBonnis and Susanna[9] also confirmed these results. They found dilatation of strips of coronary vessels in the majority of their experiments, in a few experiments, however, no influence of epinephrin being evident. Wiggers,[10] who studied the rate of outflow of blood from the coronaries in the resting heart, concluded that epinephrin caused contraction of the coronary vessels. Bond[11] and Campbell,[12] however, have been unable to demonstrate a constricting influence of this drug on the coronary vessels.

In view of the results of the large majority of these investigators, it is very probable that epinephrin does not cause a constriction of the coronary vessels, and that accordingly, it cannot interfere with the nutrition of the cardiac musculature.

We may, therefore, conclude that epinephrin does not cause a constriction of the coronary vessels, and that there exists no basis for the assumption that epinephrin produces myocarditis through its action on the coronary vessels. There are other facts which likewise seem to us to preclude such an interpretation. In the first place, whenever myocarditic lesions exist as a result of occlu-

6. Schaefer: Arch. d. sc. Biol., Suppl. Festschr. f. Pawlow, 1904, 251; Centralbl. f. Physiol., 1904, xviii, 817.
7. Langendorff: Centralbl. f. Physiol., 1907, xxi, 551.
8. Pal: Wien. med. Wchnschr., 1909, 109, p. 138.
9. DeBonnis and Susanna: Centralbl. f. Physiol., 1909, xxxiii, 139.
10. Wiggers: Am. Jour. Physiol., 1909. xxiv, 391.
11. Bond: Jour. Exper. Med., 1910, xii, 575.
12. Campbell: Quart. Jour. Exper. Physiol., 1911, iv, 1.

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sion of the coronaries, the region near the apex is affected much more frequently than the base, while the lesions caused by epinephrin are almost exclusively found at the base of the ventricle.

Furthermore, the character of the lesion does not seem to us to be compatible with such an origin. After an acute occlusion of the coronary arteries infarct-like changes are found; at a later period fibrous tissue takes the place of the injury; while in our experiments the primary changes consisted in an increase in volume of the fibers and in the number of muscle nuclei accompanied by an increase of connective tissue.

A direct toxic action of epinephrin on the heart muscle has also to be considered as a possible explanation, especially as it is very probable that the necroses found in the media of the aorta after numerous injections of epinephrin are due to a direct toxic action on the media of the vessel, and, indeed, one of us[13] upheld such an interpretation on a former occasion. Especially might such an interpretation appeal to us in cases in which, after repeated injections of epinephrin, degenerative changes are found both in the aorta and heart. Here it might be held that a toxic action has been exerted on both organs. Nevertheless, it seems to us that this explanation is not applicable in the case of our experiments, in which, after one single injection of epinephrin, marked changes were found in the heart muscle.

Again, the situation of the lesion at a place where the muscle fibers are exposed to the greatest strain after injection of epinephrin, as well as the character of the lesion in which degenerative processes in the parenchyma are not the principal changes, seem to us to make such an explanation unsatisfactory, although we do not wish to exclude a direct toxic action of epinephrin as a contributing factor. It seems to us, therefore, that in the case of the experimental lesions of the rabbit, the theory advanced by us is the most satisfactory.

13. Loeb and Gilbens: Am. Jour. Med. Sc., 1905, cxxx, 658.

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We conclude, then, that mechanical strain with its physico-chemical sequels is responsible for both the cardiac hypertrophy and myocarditic changes in the rabbit's heart.

Let us now briefly consider how far our observations and theoretical considerations are applicable to certain pathologic conditions found in man. Here, also, we find a combination of hypertrophy of the heart muscle and interstitial changes, especially increase in connective tissue in a similar manner as in the experimental lesions of the rabbit. Sometimes, the hypertrophy represents by far the more important change; at other times, the connective tissue increase is quite marked. Accordingly, these conditions are designated as hypertrophy of the heart muscle and as chronic myocarditis. In most cases, a combination seems to be present, and it is doubtful whether a sharp division between these two conditions can be maintained.

The same combination of changes is found in the experimental lesions of the heart of the rabbit. Here are noted, just as in the human heart, certain nodular areas of connective tissue overgrowth, especially at somewhat later stages, at a time when the acute lesions have retrogressed to a great extent. In the rabbit's heart we find this condition as the result of strain. The same holds good, to a great extent, in the case of the human heart. We find these changes in persons in whom the heart has to do excessive work in order to overcome increased resistance as in cases of valvular lesions, arteriosclerosis, kidney lesions. It is also possible that in cases in which, under the influence of bacterial or non-bacterial poisons, apparently a dilatation of the heart is primary, the subsequent hypertrophic and myocarditic changes owe their origin to the increase in work to which such hearts are subject in consequence of the dilatation.

There exist, however, some differences between the conditions found in the rabbit's heart and in hypertrophy and myocarditis in man. In the former, the parenchymatous degenerative changes in the muscle cells are

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more prominent than in the latter. This difference is, perhaps, due to the acuteness of the change in the heart and to the excessive strain, extending over a brief period only in the rabbit, while in man the strain is more chronic, extending over a long period and is usually less at any given time. In the latter we might, therefore, expect the hypertrophic and interstitial changes to prevail. We have, however, seen that also in the case of the rabbit the degenerative parenchymatous changes disappear relatively rapidly, leaving merely some fibrous bands. We may, therefore, assume that in man degenerative parenchymatous changes which perhaps existed at given times—and such changes are occasionally found in cases of hypertrophy—will heal within a brief period of time, leaving behind fibrous nodular bands.

Some pathologists ascribe the cardiac hypertrophy proper to the increased strain, while they interpret the interstitial changes as invariably due to the malnutrition of the muscle, caused by partial or complete occlusion of the coronary vessels. We have shown that in the case of the rabbit's heart in which changes are found similar to those in the human heart, the occlusion of the coronary vessels cannot be held responsible for the myocarditic changes. There we have a uniform cause leading to both hypertrophy and myocarditis. It seems to us that these facts suggest a similar uniform pathogenesis in many cases in which hypertrophy of the heart and myocarditis are combined in man. This, of course, does not exclude the possibility that in other cases partial occlusion of the coronary vessels is responsible for myocarditic changes, nor does it exclude the possibility that toxic substances may likewise cause myocarditic changes.

We believe that attention ought to be drawn to the similarity existing between the experimental lesions in the rabbit's heart and a large class of lesions found in the human heart, and that a similar pathogenesis may be suggested for both sets of conditions, the cardiac hypertrophy and the myocarditic changes.

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THE RELATION OF THE INTOXICATING DOSE OF HORSE-SERUM TO THE PROTECTIVE DOSE OF ATROPIN IN ANAPHYLAXIS IN THE GUINEA-PIG *

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Within the past two years Auer and Lewis[1] and Auer[2] have shown that atropin sulphate has a distinct protective action against the asphyxia of immediate or acute anaphylaxis in the guinea-pig, and their observations have been repeatedly confirmed.[3] Inasmuch as most of these studies have had for their purpose the determination of the physiology of anaphylaxis, no attempt has been made to determine the quantitative relation, if such exists, between the intoxicating dose of the serum and the dose of atropin sufficient to protect the animal from death. The study presented in this paper had for its object the determination of this point.

The problem was attacked from two sides. First, with a minimum fatal dose of horse-serum as a standard, the minimum protective dose of atropin was determined; the toxic dose of serum was then increased and the

* From the McManes Laboratory of Pathology, University of Pennsylvania, aided by a grant from the Committee on Scientific Investigation of the American Medical Association.

1. Auer, J., and Lewis, P. A.: Acute Anaphylactic Death in Guinea-Pigs, THE JOURNAL A. M. A., 1909, liii, 458; The Physiology of the Immediate Reaction of Anaphylaxis in the Guinea-Pig, Jour. Exper. Med., 1910, xii, 151.

2. Auer, J.: The Prophylactic Action of Atropin in Immediate Anaphylaxis of Guinea-Pigs, Am. Jour. Physiol., 1910, xxvi, 439.

3. Anderson, J. F., and Schultz, W. H.: The Cause of Anaphylactic Shock and Some Methods of Alleviating It, Proc. Soc. Exper. Biol. and Med., 1910, vii, 32. Biedl. A., and Kraus, R.: Die Serumanaphylaxie beim Meerschweinchen, Wien. klin. Wchnschr., 1910, xxiii, 385.

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TABLE 1.—RELATION OF MINIMUM FATAL DOSE OF SERUM TO MINIMUM PROTECTION DOSE OF ATROPIN

Number of Animal	Dose Atropin Sulphate in Gm.	Time in Minutes Between Injections	Intoxicating Dose, Horse-Serum, in C.c.	Symptoms	Result
555	0.001	10	0.2	Increased respiratory rate with dyspnea.	Recovery.
556	0.001	10	0.4	Severe	Death (5 minutes).
561	0.002	5	0.4	Marked respiratory difficulty	Recovery.
563	0.001	6	0.6	Severe	Death (5 minutes).
564	0.002	7	0.6	Marked respiratory difficulty, convulsions	Recovery.
565	0.003	6	0.8	Severe	Death (5 minutes).
569	0.007	6	0.8	Moderate respiratory difficulty	Recovery.
570	0.008	6	1.0	Severe	Death (1 minute).
571	0.010	6	1.0	Severe	Death (8 minutes).
573	0.015	6	1.0	Severe	Death (5 minutes).
577	0.020	3	1.0	Severe	Death (30 minutes).
579	0.025	3	1.0	Moderate respiratory difficulty	Recovery.
580	0.030	3	1.5	Severe	Death (5 minutes).
585	0.040	5	1.5	Severe	Death (5 minutes).
...	0.040	..	...	Moderate increase of respiratory rate	Rapid recovery.
...	0.050	..	...	Rapid cessation of respiration	Death (5 minutes).

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TABLE 2.—RELATION OF MAXIMUM NON-FATAL DOSE OF ATROPIN AND MAXIMUM DOSE OF SERUM AGAINST WHICH ATROPIN IS PROTECTIVE

Dose Atropin Sulphate in Gm.	Time in Minutes Between Injections	Intoxicating Dose of Horse-Serum in C.c.	Symptoms	Result
0.015	5	1.5	Severe	Death (5 minutes).
0.015	5	1.0	Marked respiratory difficulty; convulsions; coma	Recovery. (Death, 18 hours).
0.012	5	1.0	Severe	Death (5 minutes).
0.012	5	0.8	Severe	Death (5 minutes).
0.012	5	0.7	Marked respiratory difficulty, but without complete cutting off of air supply	Death (6 minutes).*
0.012	5	0.6	Moderate respiratory difficulty; slight general convulsions	Recovery.
0.010	5	0.6	Severe	Death (17 minutes).
0.010	5	0.5	Severe	Death (8 minutes).
0.010	5	0.4	Severe	Death (5 minutes).
0.010	8	0.3	Marked respiratory difficulty; convulsions	Recovery. (Death, 18 hours).
0.008	5	0.3	Marked respiratory difficulty; frothing at nose; convulsions	Death (18 minutes).
0.008	5	0.2	Same symptoms as preceding	Recovery.
0.006	5	0.2	Slight respiratory difficulty	Recovery.
0.004	5	0.2	Marked respiratory difficulty; convulsions	Recovery.
.....	.	0.2	Severe	Death (3 minutes).
0.018	.	...	General convulsions; respiratory failure	Death (5 minutes).
0.015	.	...	General twitching; increased respiratory rate	Recovery.

* Apparently result of exhaustion rather than anaphylaxis.

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minimum protective dose of atropin again determined, this procedure being repeated until the dose of atropin became so large as to be markedly toxic for the animal. Second, a maximum dose of atropin, just short of the lethal dose for the animal, was administered and a determination made of the largest amount of horse-serum against which the dose of atropin protected the animal; the dose of atropin was then diminished and the maximum nonfatal dose of serum again determined. This procedure was continued until a point was reached where further reduction in the size of the dose of serum would in itself have failed constantly to produce death. Throughout the study a constant sensitizing dose of 0.05 c.c. of horse-serum was used. After a lapse of sufficient time for the animals to become actively hypersusceptible the dose of atropin was given into the exposed right jugular vein and the intoxicating dose of horse-serum three to ten minutes later into the same or opposite vein. All animals were closely observed in their cages and autopsies performed on those that died. It was found in the latter that the lungs were somewhat more congested than is the rule with typical anaphylaxis;[4] the myocardium often showed punctate hemorrhages, and the abdominal viscera were much congested but free from macroscopic hemorrhage.

The first phase of the study occupied about a month. For this reason the second injection of serum with its corresponding dose of atropin was given from twenty-five to fifty-five days after sensitization, the larger doses being given in the later periods. In the second series, however, the work progressed more rapidly, the time of sensitization being from seventeen to eighteen days; furthermore, the order of experiment was reversed in the second series, the larger doses being administered first. Any objection that might be raised on account of the varying time of sensitization in the first series is certainly overcome by the method of the second.

4. Karsner, H. T.: Die Lungen in Anaphylaxie und in Anaphylaxie gleichenden Zuständen, Ztschr. f. Immunitätsforsch., in press.

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Table 1 presents the essential results of the first series of experiments. It is seen that the minimum fatal dose of horse-serum (0.2 c.c.) was insufficient to produce death when preceded by the administration of 0.001 gm. of atropin. In order to protect against 0.4 c.c. and 0.6 c.c. of horse-serum, it was necessary to increase the dose of atropin to 0.002 gm. To protect against 0.8 c.c. serum, 0.007 gm. atropin was necessary and against 1 c.c. serum, 0.25 gm. was needed. No dose sufficiently large to protect against 1.5 c.c. serum was possible, for before such a point was reached the animals succumbed to the dose of atropin. The presence of distinct symptoms of anaphylaxis in all those animals which were saved, is sufficient evidence of the fact that they were highly sensitive. It is clear then that there is a quantitative relation between the protective dose of atropin and the intoxicating dose of horse-serum.

The second series is presented briefly in Table 2. Whereas the atropin used in the first series was from Smith, Kline, French & Co., that used in the second series was from Merck & Co. This fact probably accounts for the variance in absolute dosage of atropin seen in the two tables, for the animals of the two series were from the same general stock. Eighteen milligrams of atropin killed a guinea-pig within five minutes. It is seen that 0.015 gm. protects against 1 c.c. serum, 0.012 gm. against 0.3 c.c. serum, and 0.004 gm. against 0.2 c.c. serum. The minimum protective dose of atropin was not determined. The conclusion that there is a general relationship between the doses of atropin and serum is obvious. From the first series, it appeared that the curve of the dose of atropin rises much more rapidly than that of the dose of horse-serum, but this is not borne out by the results of the second series. That any such exact relationship could be demonstrated, was doubtful from the first because of slight variance in the individual susceptibility to the horse-serum. The same slight individual difference of response is seen in connection with the administration of atropin.

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THE USE OF REBREATHING IN THE ADMINISTRATION OF ANESTHETICS

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Since the very introduction of ether and chloroform the use of rebreathing in administering them has been under discussion. With chloroform it has seldom been permitted, while with ether until recent years it was considered desirable,[1] and ether was given almost exclusively by means of a closed inhaler of some sort. Since the introduction of the open method of etherization, however, rebreathing has fallen into disfavor, and writers now pretty generally condemn it.[2] It is my purpose to show that, contrary to this common opinion, rebreathing when properly regulated and when the oxygen supply is ample is harmless and can be put to a valuable use. The evidence in favor of this is derived partly from a series of 2,500 gas-oxygen and gas-oxygen-ether anesthesias given by a closed method at Professor Halsted's clinic, and partly from the recent and very important work of the physiologists — Henderson,[3] Hill,[4] Haldane[5] and others — on the carbon-dioxid metabolism of the body. In a preceding paper[6] I have discussed the use of

1. Hewitt: Anesthetics and Their Administration, Ed. 3, p. 329.
2. Cunningham and Anderson: Methods of Administering Ether, THE JOURNAL A. M. A., Nov. 7, 1908, p. 1574.
3. Henderson: Acapnia and Shock (a series of papers), Am. Jour. Physiol., 1908, xxi, 126; 1909, xxiii, 345; 1909, xxiv, 66; 1910, xxv, 310; 1910, xxv, 385; 1910, xxvi, 260; 1910, xxvii, 152.
4. Hill and Flack: The Effect of Excess of Carbon Dioxid and of Want of Oxygen on the Respiration and the Circulation, Jour. Physiol., June 30, 1908; The Influence of Oxygen Inhalations on Muscular Work, Jour. Physiol., July 1, 1910.
5. Haldane and Poulton: The Effects of Want of Oxygen on Respiration, Jour. Physiol., 1908, xxxvii, 390.
6. Gatch: Nitrous Oxid-Oxygen Anesthesia by the Method of Rebreathing, THE JOURNAL A. M. A., March 5, 1910, p. 775.

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rebreathing in giving nitrous oxid with oxygen; here I wish to consider its use in administering any inhalation anesthetic, and more especially ether.

The subject can be approached most simply by considering the harmful results supposed to follow the administration of ether by the use of closed masks. I shall speak only of ether for the present, because most of the investigations bearing on the question of rebreathing have had to deal with this anesthetic. The ill effects in question may be grouped under two heads:

1. Injury to the lungs.
2. General toxic effects.

Dreser,[7] Offergeld,[8] Poppert[9] and Hölscher[10] have studied very carefully the effects of ether vapor on the respiratory passages. Dreser regards any concentration of vapor which cannot be inhaled by the patient while in the conscious state without discomfort and coughing as harmful to the lungs. Applying this test, he fixed on 6 per cent. to 7 per cent. as the highest concentration which should be used. Offergeld, experimenting on animals, found that the lungs after etherization by a closed method showed much graver injuries than after etherization by an open method. With the closed method he found extensive fatty degeneration and desquamation of the epithelium of the air-passages, also many minute hemorrhages into the alveoli; many of the animals died of bronchopneumonia. With the open method the pulmonary lesions were of a comparatively unimportant character, unless the administration was frequently repeated at short intervals. Poppert, whose experiments were similar to Offergeld's, concluded that ether vapor is more irritating to the lungs the greater its concentra-

7. Dreser: A Contribution to the Study of Anesthesia by Ether, Bull. Johns Hopkins Hosp., January, 1895.
8. Offergeld: Lungenkomplicationen nach Aethernarkosen, Arch. f. Chir., 1907, lxxxiii, 505.
9. Poppert: Experimentelle und klinische Beiträge zur Aethernarkose und zur Aether-Chloroform-Mischnarkose, Deutsch. Ztschr. f. Chir., lxvii, 505.
10. Hölscher: Experimentelle Untersuchungen über die Entstehung der Erkrankungen der Luftwege nach Aethernarkose, Arch. f. klin. Chir., 1898, lvii, 175.

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tion. Hölscher studied the distribution of secretion in the air-passages during ether narcosis. He found that there is only a very slight secretion from the epithelium situated below the level of the larynx. By putting coloring materials into the mouths of anesthetized animals he proved that mucus and saliva may be aspirated into the deepest air-passages. His conclusion was that "affections of the air-passages occurring after ether are for the most part due to the aspiration of infectious mouth contents."

We can summarize the experimental results dealing with the effects of ether vapor on the lungs as follows:

1. The irritant action of the vapor varies according to its concentration.

2. Postoperative lung complications are frequently caused by the aspiration of mouth contents.

3. The greater severity of the pulmonary lesions found after experimental etherizations by the closed method can be satisfactorily accounted for by the great concentration of ether vapor in the closed masks and the greater liability to aspirate mouth contents when these are used.

We now have to consider why the general toxic effects which follow ether anesthesia are more severe after the closed method than after the open method. Writers are almost unanimous in asserting that they are so. The work of Ladd and Osgood[11] is very important in this connection. These authors studied the frequency of postanesthetic vomiting in patients after etherization with the Blake cone and in those etherized by the "gauze ether" method. Vomiting was much more frequent and severe among the former patients than among the latter. With the Blake cone cases they found acetone in the urine after operation in 88 per cent. of the cases, while with the "gauze ether" cases they found it in only 26 per cent. The technic and advantages of the open

11. Ladd and Osgood: Gauze Ether. Ann. Surg., September, 1907.

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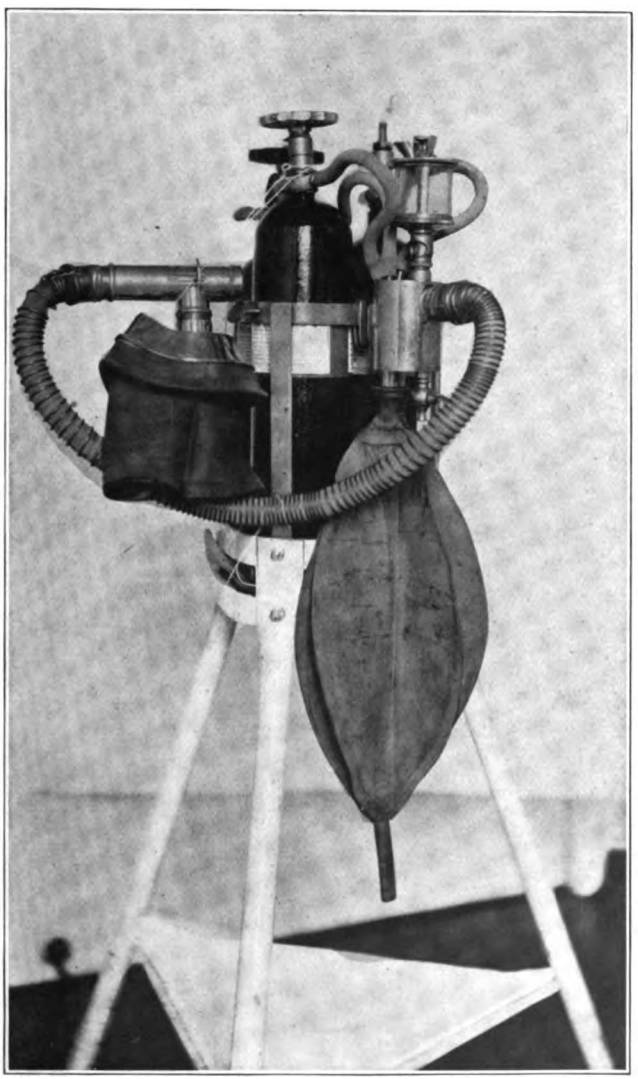

Fig. 1.—Apparatus for administration of anesthetic.

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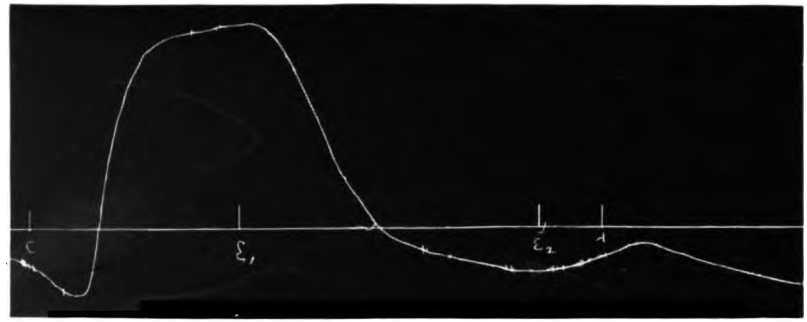

Fig. 2.– Tracing obtained from the pyloric ring of a frog suspended in a moist chamber into which ether vapor and carbon dioxid could be passed. At C, carbon dioxid was passed over the muscle, causing a sharp contraction. At E_1 very dilute ether vapor was turned on with the carbon dioxid, causing immediate relaxation. At E_2 the ether was turned off.

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method are discussed by Miss Magaw,[12] who reports 14,000 cases with most satisfactory results. In short, there is no doubt that this method of etherization is better than the rather crude closed methods it has replaced. Of its disadvantages and dangers I shall speak later.

To what causes are the ill effects which follow the closed method to be traced? The causes commonly held responsible are the following[2]: (1) anoxemia, (2) overconcentration of ether vapor, (3) toxic organic substances in the expired air, and (4) excess of carbon dioxid in the expired air. The first and second of these possible causes are, I believe, the real ones. The third is imaginary, since the physiologists have demonstrated beyond any reasonable doubt that there are no organic poisons in the breath.[13] Concerning the excess of carbon dioxid, it is the purpose of this paper to show that it is harmless, and can be put to a valuable use.

It is perfectly evident that anoxemia and overdosage of ether, evils almost unavoidable when this anesthetic is given in a tightly closed mask, must do harm. We know that a deficiency of oxygen will quickly cause the gravest injuries to the tissues. Dreser found that the gas within closed etherizing masks would at times put out a burning candle! He also found that the ether vapor within the closed masks sometimes reached a concentration as high as 34 per cent., while 6 to 7 per cent. is the greatest concentration which can be inhaled without irritation to the air-passages. With such an overdosage of ether as this it is true that the excess of carbon dioxid within the closed masks is injurious, for

12. Magaw, Alice: A Review of Over 14,000 Cases of Surgical Anesthesia, Surg., Gynec. and Obst., 1906, iii, 795.

13. Crowder, Thomas R.: A Study of the Ventilation of Sleeping-Cars, Arch. Int. Med., Jan. 15, 1911, p. 85; Haldane and Smith: The Physiologic Effects of Air Vitiated by Respiration, Jour. Path. and Bacteriol., 1892 and 1893, pp. 1, 168, 318; Heyman, Paul, Ercients, Flügge: Report of Experiments at the Institute of Hygiene at Breslau, Ztschr. f. Hyg., 1905, xlix, pp. 363, 388, 405 and 433; Hill and Walker: The Relative Influence of the Heat and Chemical Impurity of Close Air, Jour. Physiol., Nov. 9, 1910.

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it stimulates powerfully the respiration and leads quickly to an overabsorption of ether by the blood.

If the truth of what has just been stated be admitted, it follows that if we can prevent anoxemia, overconcentration of vapor, and too great a depth of anesthesia, we can obviate most of the serious objections to the closed method of giving ether.

I have so far limited the discussion to the administration of ether, but it will apply, in part at least, to all anesthetics given by inhalation—to chloroform, ethyl chlorid and nitrous oxid. With all of these it is evident that anoxemia must be prevented. With chloroform and ethyl chlorid, on account of their great toxicity, overdosage is the most important problem in administration. With nitrous oxid, in the absence of asphyxia overdosage is impossible. Ether requires a special consideration on account of the peculiar irritant action of high percentages of its vapor on the lungs and air-passages.

I have made use of the principles laid down in the foregoing paragraphs in developing a method of anesthesia, the technic and advantages of which I now wish to describe. Nitrous oxid and, if necessary, ether are the anesthetics used. The apparatus employed[14] consists essentially of a mask connected by a piece of flexible tubing to a rubber bag. This forms a closed space into which the patient breathes. On the mask is a valve-box by means of which the patient can be made to breathe to and fro into the bag, or to inspire from the bag and expire into the air, thus emptying the latter. The bag is attached to a small box, through which the current of gas must pass back and forth from the bag to mask. Into this box nitrous oxid and oxygen are admitted, and ether, drop by drop, from a receptacle above. The ether is vaporized in the box from a series of drip plates, and

14. I have already described the apparatus elsewhere in some detail (Note 6). It will be noted that the arrangement for giving ether has been changed so as to permit of a more accurate dosage. The method of administration is practically unchanged, except that I now allow rebreathing for somewhat longer intervals.

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any excess of ether can be drained off at once by a stopcock. The method of administration is simple. The mask is adjusted carefully to the patient's face and the bag filled with nitrous oxid containing a very small amount of oxygen. The patient is made to breathe this mixture in and out through valves, thus replacing all the air in his lungs with nitrous oxid and oxygen. The bag is next refilled with the same mixture of gases which the patient is now made to rebreathe for from five to eight minutes. At the end of this time he is allowed to empty the bag, breath by breath, into the air, after which it is refilled, and the same procedure is repeated. Oxygen is given, without any attempt to estimate its exact percentage to the nitrous oxid, in quantities just sufficient to keep the patient's color free from cyanosis. If desired, nitrous oxid can easily be given under positive pressure, by keeping the bag slightly overdistended. This is sometimes a useful procedure in managing difficult cases. Anesthesia is usually established in less than two minutes. If the anesthesia is unsatisfactory with nitrous oxid alone, ether is added. This combined nitrous oxid-ether anesthesia has many points of practical and scientific interest and calls for a special consideration.

Ether is not given till the patient's respiration has been stimulated by the accumulation of carbon dioxid which results from the rebreathing. It is then added drop by drop. The heated gases quickly evaporate it from the drip plates, and it is rapidly absorbed by the blood because of the increased pulmonary ventilation. The most difficult subjects can thus be deeply anesthetized.

I have already referred to Dreser's experiments in which he proved that from 6 to 7 per cent. of ether vapor is the greatest concentration which can be inhaled by a patient in the conscious state without irritation and coughing. Precautions must be taken to keep the concentration of ether vapor in the mixture of gases below

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this level if we wish to do away with any possibility of injuring the lungs. This is quite easily accomplished, as the following simple calculation will show. The gas-bag moderately distended holds about 10 liters of gas, the mask and tubing hold about 1 liter, and the entire respiratory system of the patient holds about 3 liters. When the patient is rebreathing, these all form one closed space with a total capacity of about 15 liters. Our problem is this: How much ether must be added to 15 liters of gas to make the concentration of ether vapor 7 per cent.? Professor Abel has very kindly performed this calculation for me and gives the amount of ether as 4.2 c.c. He desires me to state, however, that the conditions of the problem are so variable that the amount of ether required cannot be determined with absolute accuracy. The varying temperature in the apparatus, the loss of ether through leaks and by absorption in the lungs are factors for which no accurate data can be furnished. But absolute accuracy is not necessary, because the constant loss of ether gives us a wide margin of safety so that we can probably add ether much faster than our calculation allows without exceeding the danger limit.

With the drops of ether falling at the rate of 120 to the minute I have found that it takes two and one-quarter minutes to add the 4.2 c.c. Therefore, if we give ether at this rate and take precautions not to keep it dropping for more than two minutes at any one time, and to keep the bag constantly full of gas, we can be sure that the ether vapor will not reach a concentration greater than 7 per cent. If the anesthetist does not care to follow some such rule as this he can easily, and I think with perfect safety to his patient, estimate the strength of ether vapor by its odor as it escapes from the valve-box. In fact, ether is usually given for so short a time that even if it were administered in a somewhat concentrated form it would probably do no harm.

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It has been found unnecessary to give ether constantly during the administration. When enough has been given to produce satisfactory anesthesia, this can be maintained with nitrous oxid alone, even in cases requiring a deep narcosis. This is to be explained by the fact that the rebreathing prevents the ether, once dissolved by the blood, from being thrown off as rapidly as it would otherwise be by the lungs, which are the organs by which it is practically all eliminated.[15] Suppose, for example, that a patient having a certain amount of ether dissolved in his blood is given some fresh nitrous oxid and oxygen to rebreathe. The ether will be thrown off from his lungs till the tension of its vapor in the gases being breathed will equal that in the blood. When this occurs no more ether will be eliminated until a new supply of gas is furnished.

Not only can we prevent the elimination of ether by rebreathing, but we can also hasten the elimination by a rapid ventilation of the lungs with fresh gas. During the process of rebreathing, carbon dioxid accumulates in the body and stimulates the respiratory center so that the breathing becomes deep and rapid — often fifty or sixty respirations to the minute. When a patient, anesthetized in the way I have described and breathing at such a rate, is given a fresh supply of gas and allowed to discharge each breath into the air, he apparently rapidly rids himself of the small dose of ether he has been given. Thus it is possible to anesthetize a patient so deeply that he will not stir during a Whitehead operation, and yet have him conscious before leaving the operating room. By careful administration we can in most cases keep the patient from knowing that he has been given any ether at all, so complete and rapid is its elimination.

I would suggest that this method of removing a volatile anesthetic by rapid ventilation of the lungs be used

15. Hewitt: Anesthetics and Their Administration, Ed. 3, p. 50; Cushny: Pharmacology and Therapeutics, Ed. 4, p. 166; Cushny: The Exhalation of Drugs by the Lungs, Jour. Physiol., xl, 17; Nicloux: Elimination de l'éther contenu dans le sang après l'anesthésie pendant la période de retour, Cont. rend. Soc. biol., 1907, i, 8.

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at the close of every administration of chloroform or ether. The increased pulmonary ventilation can be easily brought about by making the patient breathe in and out, through valves, air or oxygen containing a small percentage of carbon dioxid. I have had such a mixture of oxygen and carbon dioxid prepared which contains 7 per cent. carbon dioxid, but have not had the opportunity to give it a clinical trial.

In this connection it is interesting to consider the effect which morphin has on the elimination of ether or chloroform from the body. Morphin decreases markedly the rate of pulmonary ventilation.[16] Large doses of it must therefore retard the elimination of the anesthetic and thus increase its toxic action. It is often possible to detect the odor of ether or chloroform on the patient's breath for several hours after operation. This slow excretion may be due, in part at least, to the morphin, a hypodermic of which is necessary before or after almost every anesthesia. Perhaps this effect of morphin can be prevented by means of the method I have just described for quickly eliminating the anesthetic.

In the preceding paragraphs I have discussed how ether can be safely introduced and speedily removed from the patient's system. During its stay therein we are powerless to prevent its toxic action. By giving it, however, in combination with nitrous oxid and morphin we can reduce its dose, and therefore its ill effects, to the minimum, since the major portion of the anesthesia is produced by the other two drugs. It is probable also that the effect of ether when thus administered with other narcotics is relatively much greater than when given alone, as it is well known that narcotic drugs given in combination reinforce one another's action.[17] Thus the powerful joint effect of morphin and scopolamin has been explained.

16. Cushny: Pharmacology and Therapeutics, Ed. 4, p. 211.
17. Führer: Pharmakologische Untersuchungen über die Mischnarkose, München. med. Wchnschr., 1911, No. 4; Bürge: Die Wirkung von Narkotikakombinationen, Deutsch. med. Wchnschr., 1910, Nos. 1 and 2, pp. 20 and 62.

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I shall devote the remainder of this paper to matters of direct clinical interest. The form of anesthesia herein described has now been in use in the surgical clinic of the Johns Hopkins Hospital for two years. Here over 2,500 patients have been anesthetized by this method. It is now our routine form of anesthesia for all operations except those on the face, upper air-passages or cranium. In these we have found it inconvenient on account of the difficulty of keeping the mask in place.

Before operation the patient is given an enema and deprived of food for several hours, but is allowed to take small quantities of water. About thirty minutes before the anesthesia is begun he is given a hypodermic of morphin and atropin, the dose for an adult being morphin one-sixth grain, atropin 0.01 grain. The anesthesia is started after the patient has been placed on the table and while the field of operation is being surrounded by sterile towels. It is established so quickly that the incision can usually be made in two minutes after the mask has been put on. Any depth of anesthesia which the condition of the patient and the nature of the operation may require can be easily obtained, because of the control of the patient's respiration which is given by the rebreathing. In abdominal operations, if the increased activity of the respiration is inconvenient, it can be prevented by giving a fresh supply of gas at frequent intervals. The bleeding during gas-oxygen or gas-ether anesthesia is about the same as during open ether anesthesia. The patient's temperature, provided he is kept dry and covered, will be found elevated from 0.5° to 2° after an hour's operation. With light narcosis under nitrous oxid and oxygen alone, the pulse may be rapid (from 140 to 160 to the minute) but this is of no significance provided it is regular and of good quality, and there is no hemorrhage. The rapid heart-rate decreases when ether is given.

This form of anesthesia is especially well suited for long operations. In fact the anesthesia does the patient

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so little harm that within reasonable limits the duration of the narcosis need not be considered. The surgeon can therefore operate with a deliberation and attention to detail that would otherwise be unjustifiable. The following typical cases show the truth of this contention:

Case 1.—The patient was a negro man, aged 27, in good physical condition. Operation: Excision of a sarcoma from the right popliteal space, and blood-vessel transplantation. Duration of anesthesia, five hours. The pulse-rate per minute varied from 72 to 100. The blood-pressure at the end of four hours of anesthesia was 130 mm. of mercury. The patient regained consciousness before leaving the table. He had no headache, nausea or vomiting, though he was given water at once. His urine after operation contained no albumin or acetone. He was allowed to rebreathe at two and one-half and three-minute intervals. The narcosis was deep and quiet. Ether was given with the gas for the first half hour.

Case 2.—The patient was a white woman, aged 30, in rather poor condition. Operation: Resection of the ascending and transverse colon. Duration of anesthesia two hours and five minutes. No ether was used. The narcosis was light, the patient at times moving her limbs. Recovery was immediate and unattended with headache or vomiting.

Case 3.—The patient was a colored woman, aged 30, in good condition. Operation: Excision of the right breast, pectoral muscles and axillary glands for advanced cancer of the breast, Thiersch skin grafting of the raw surface of the breast. Duration of anesthesia, three hours and fifty-five minutes; 2½ ounces of ether, 130 gallons of gas and 30 of oxygen were used. The anesthesia was quiet and satisfactory, the recovery immediate and without headache, nausea or vomiting.

I could report many more cases similar to the above, but these show sufficiently well how little the patient is injured by this form of anesthesia. A word of caution is, however, necessary. This is that during any administration, and especially during a long administration, the patient's breathing must be kept free and unobstructed, and his color good. If a patient has to work hard for every breath he soon wears himself out. The color of the blood in the wound, the hue of the patient's face, and the character of his breathing as shown by the move-

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ments of the rubber bag are the best indicators of his condition. The surgeon himself can hardly fail to notice these. If the patient's breathing cannot be kept unobstructed the use of the apparatus should be abandoned at once and some other method of anesthesia used.

We have had three fatalities, during or immediately after operation, in our series of 2,500 cases. How much the anesthesia was to blame for these may be judged from the following reports:

FATALITY 1.—The patient was a colored woman, aged 44, with exophthalmic goiter of four years' standing. She had an irregular, intermittent pulse, the rate of which had been between 120 and 140. Her heart was enlarged, and she had ascites and edema of the ankles. During the last week of her life she had several severe attacks of dyspnea, associated with extreme rapidity and irregularity of the pulse. For these she was given a course of digitalis, which improved her condition so much that it was thought she could withstand a partial thyroidectomy. When the mask was placed over her face, she made a very slight struggle and took several shallow breaths. The operator then saw the superficial veins of her neck suddenly dilate. This apparently marked the time of death, and occurred within half a minute of the time the anesthetic was started.

FATALITY 2.—The patient was a man with aortic and mitral insufficiency, on whom it was proposed to do a perineal prostatectomy. He was given ether with the gas and oxygen. The anesthesia went very well till the patient was placed on the perineal table with his buttocks elevated; then he became cyanotic and died. An immediate autopsy revealed the presence of a large pericardial effusion, the presence of which had not been recognized before operation.

FATALITY 3.—The patient was a girl of 16, with multiple infectious arthritis; general condition poor. Operation: Injection of both knees with oil and manipulation of knees, ankles and elbows. Duration of anesthesia fifteen minutes. The anesthesia was uneventful, except for a marked increase in pulse-rate while each joint was being manipulated. At no time was the breathing obstructed. At the close the pulse-rate went up very rapidly; the color became cyanotic and could not be cleared up with oxygen. The breathing became weaker and weaker and finally ceased.

An autopsy showed a very large thymus and hypertrophy of all the lymphatic tissues. The pathologists gave status lymphaticus as the cause of death.

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The first and second of these patients had circulatory disease of such gravity that the anesthesia is not to be seriously blamed for the deaths. How the third fatality was brought about I am at a loss to understand. The toxicity of nitrous oxid is certainly too low to have caused it.

Notwithstanding these fatalities I believe that this form of anesthesia properly employed is well suited for cardiac cases. Two cases of cesarean section performed by Prof. J. W. Williams on women with serious valvular lesions will show the grounds for this belief. Both women were in about the seventh month of pregnancy, and in both delivery was necessary to save the life of the patient. One of the two was *in extremis* and her death on the table was regarded by the operator as probable. Both women had such urgent dyspnea that the anesthetic had to be started with the patient sitting upright. The same method of administration was employed in both cases. Each patient was given a hypodermic of morphin large enough to quiet her. In inducing anesthesia great care was exercised to avoid the least excitement or struggling on the part of the patient. Both were allowed to rebreathe oxygen till the respiration was stimulated before any nitrous oxid was given. Enough ether was used to give a quiet anesthesia. The operations were performed with the patients' bodies elevated at an angle of 20° to 30°. The pulse of both patients was much better during anesthesia than before, and the operator was able to proceed without undue haste. Both patients made an excellent recovery.

I have hitherto spoken of the advantages of an excess of carbon dioxid in the blood — a hypercapnia — during anesthesia. Our clinical experience has certainly shown that this, to the degree we permit, is harmless. Hill and Flack[4] state that "the effects of carbon dioxid on the heart can always be quickly recovered from, even if the blood-pressure has sunk to zero." These authors found that carbon dioxid up to a percentage of 35 in the air

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breathed stimulates the respiration, while above 35 it depresses it; also that percentages up to 22 produce a rise in blood-pressure, while higher percentages cause a fall. Of course it is impracticable to determine exactly what percentage of carbon dioxid a patient is breathing. The anesthetizer must regulate the time of rebreathing so that the patient's respiration is moderately stimulated. The periods of rebreathing for 10 liters of gas range from three to five minutes, any leakage from the apparatus being meanwhile made good by the addition of fresh gas.[18]

Does a deficiency of carbon dioxid in the blood —acapnia—do serious harm? The work of Henderson[3] on this problem is so well known as to require no more than a reference here. He has been able to reduce animals to a state of extreme shock by overventilation of their lungs. He asserts that acapnia causes complex osmotic changes in the tissues, which result in a passage of water from the blood into the lymph and into the tissue-cells and a dilatation of the finer veins. Interference with the normal filling of the right side of the heart by this process is the essential phenomenon in surgical shock. In extreme cases of acapnia the blood-stream is so scant and the respiration so feeble that the tissues do not receive the necessary amount of oxygen. An asphyxial acidosis results which does the body-cells irreparable injury. Whether we accept Henderson's theory or not we must admit that the accumulation of carbon dioxid by the process of rebreathing is an efficient stimulus to the respiration and circulation. In fact we use it as a purely therapeutic measure in cases of morphin poisoning, in cases of so-called traumatic or toxemic shock,[19]

18. After rebreathing 10 liters of oxygen for three minutes, I found it to contain 8.9 per cent. CO_2. Allowing for decreased CO_2 formation during anesthesia, it is probable that the percentage breathed by the patient is seldom above this.

19. Patients with feeble pulse and respiration—so-called "shock" cases—should be made to rebreathe air in oxygen till their respiration is normal before breathing the anesthetic.

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and wherever the respiration is feeble.[20] Oxygen can be given much more effectually and cheaply by the use of rebreathing than in the ordinary way. Thus with anesthetics of low toxicity and the use of rebreathing we can sometimes actually benefit a very ill patient by an anesthesia.

On the other hand, when we give ether by the open method we take a very efficient means of producing acapnia, because ether diminishes the formation of carbon dioxed by the tissues, and by stimulating the respiration hastens its elimination as well. Symptoms of a mild grade of acapnia under open ether anesthesia are common. Thus a patient who has perhaps been difficult to anesthetize or who has been lightly under ether for some time and is breathing at a rapid rate will gradually stop breathing. After an interval of perhaps two or three minutes his respiration will start again but will not be normal for a long time. This occurrence, though alarming, is usually followed by no harmful results. Of course hundreds of patients are etherized daily by the open method without developing symptoms of shock. What prevents a serious grade of acapnia in the great majority of cases? There are a number of things which do so. In the first place many anesthesias are of too brief duration for acapnia to develop. Then again there is frequently more or less obstruction to the breathing during narcosis, and this prevents acapnia. Likewise the slowing of the respiration which results from a preliminary hypodermic of morphin may protect from the same danger.[21] Finally, the so-called "open" method is usually not "open" at all, for the mask is so covered with towels or gauze that the patient does considerable rebreathing.

It is a pity that in a case like the following accurate determination of the amount of carbon dioxid in the

20. Levi, Ettore: Studies on the Patho-Physiologic Action of CO_2 and on the Therapeutic Applications in Surgery and Medicine of Mixture of O_2 and CO_2, Estr. d. Rev. crit. di clin. med., 1910, xi, 30 and 31.

21. Crile: The Blood-Pressure in Surgery, p. 281.

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blood could not be made, so that we could judge whether or not death was due to acapnia:

The patient was a well-nourished middle-aged woman, with no disease of the heart or blood-vessels, on whom a colostomy and an excision of the rectum was done for a carcinoma. The anesthesia was by the "drop ether" method and was of two hours' duration and rather light. The patient's breathing was rapid and carefully kept free from obstruction. There was practically no loss of blood and but little trauma connected with the operation. The patient never regained complete consciousness, though she could respond feebly when spoken to. Her pulse was rapid and of poor quality; her temperature subnormal, her color slightly cyanotic and her respiration very feeble. She never rallied, and died eight hours after operation. An autopsy showed no apparent reason for death, which was attributed to surgical shock.

Is it not possible in this case that an acapnia had produced fatal injuries to the tissues in the manner described by Henderson?

Apart from the prevention of acapnia the form of anesthesia I have described has several other advantages over open ether anesthesia. The chief of these are three: (1) lessened postanesthetic vomiting; (2) decrease in number of cases of abdominal distention after operation; (3) practical abolition of postanesthetic lung complications.[22]

Vomiting after operation, of course, depends on many things besides the anesthetic. About 35 per cent. of our patients vomit, but the vomiting is usually very little. In looking over the special charts of 200 patients I found only four who had had more than very transient vomiting. Of the cases one was a case of exophthalmic goiter, one a case of stone in the common bile-duct, one a case of spreading peritonitis from an appendix abscess, and one a case of intestinal resection. The nausea alone seldom prevents a patient from taking water and nourishment at once after operation.

There has been very little experimental work on the question of abdominal distention following ether anes-

22. Homans: Post-Anesthetic Pulmonary Complications, Bull. Johns Hopkins Hosp., April, 1909.

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thesia. Cannon and Murphy[23] observed a great delay in the emptying of the stomach contents into the duodenum, and a slowing of the passage of food along the intestines after etherization. Figure 2, which is a tracing obtained from Dr. D. R. Hooker,[24] demonstrates the paralyzing effect of a weak ether vapor on the pyloric

23. Cannon and Murphy: The Movements of the Stomach and Intestines in Some Surgical Conditions, Ann. Surg., April, 1906, xiii, 513.

24. I wish to thank Dr. Hooker for permission to publish this tracing and for the following note:

"Dr. Gatch has asked me to add a note covering some unpublished experiments done in the physiologic laboratory of the Johns Hopkins University, which appear to have a direct bearing on his own work.

"Cross-sections of blood-vessels or intestine, to which a recording lever was attached, were hung in a moist chamber. In the use of tissue from warm-blooded animals the temperature of the chamber was maintained constant at 35 C. Through the chamber were passed alternately streams of oxygen and carbon dioxid gas. By this method the tissue studied was exposed to practically pure atmospheres of the gases. The experimental conditions, therefore, did not fall within physiologic limits, so far as the percentage of gas is concerned. Work is now in progress to investigate the effect of different percentages of oxygen and carbon dioxid. Aside from the result of this future work, however, the interesting fact has been demonstrated that the musculature of the blood-vessels responds in atmospheres of the gases, studied in an exactly opposite manner to the musculature of the intestines. Carbon dioxid causes a marked improvement in the tone of the intestines and a marked relaxation of tone in the veins and arteries. On the other hand, oxygen causes a relaxation of tone in the intestines and an improvement of tone in the veins and arteries. These results were obtained in the case of both warm-blooded and cold-blooded animals and demonstrated with graphic records.

"If it be true that Henderson reasoned by analogy from the behavior of the smooth muscle in the intestine to that in the blood-vessel (especially the veins) in developing the acapnia theory of surgical shock, it is obvious from these results that his reasoning was not entirely justifiable.

"The correlation of the difference in action of these gases in physiologic economy tempts speculation. The body seeks to rid itself of any excess of carbon dioxid. Jerusalem and Starling (Jour. Physiol., 1910, xl, 279) have shown that carbon dioxid (0.625 of an atmosphere) increases the efficiency of the isolated mammalian heart chiefly by improving its diastolic relaxation. Bayliss (Jour. Physiol., 1901, xxvi, 32) has shown that this gas relaxes vascular tone. It has long been known that in the intestine the same gas increases peristalsis and Mall (Johns Hopkins Hosp. Rep., 1896, i, 37) has suggested that rhythmic movements of the intestines may help to empty the venous plexuses in the walls and thus aid in driving the blood into the portal system. We have, therefore, a coordination of activity which greatly facilitates the circulation of blood and the consequent rapid elimination of the carbon dioxid. Oxygen in excess, on the contrary, would tend to bring about opposite effects with a resultant retardation of the circulation.

"In conclusion, it should be clear to the reader that this is a chemical regulation of the circulation entirely peripheral in its action. The action of the gases on the medullary centers is a wholly different question."

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ring of the frog. It also shows that carbon dioxid acts as a powerful stimulant to the muscle of the ring. Of course the conditions to which the bowel was subjected when this tracing was obtained were abnormal, still the paralysis by ether is exactly what any clinician would expect. It is well recognized that an excess of carbon dioxid in the blood promotes peristalsis, and Henderson[25] has shown that the normal intestinal movements, which cease after a laparotomy, can be restored by passing a stream of carbon dioxid over the exposed bowel. These experimental results are confirmed by our clinical experience. It will be recalled that we use the smallest possible amount of ether, and produce a hypercapnia by making the patient rebreathe. In the 200 cases referred to above there was not a case of abdominal distention except after laparotomy, and among the laparotomies, seventy-five in number, it occurred in but three cases, these being the same patients who had considerable vomiting.

In 2,500 cases of gas-oxygen or gas-oxygen-ether anesthesia we have had but one case of postanesthetic pneumonia; this was in a girl with general peritonitis, who recovered. I am perfectly aware that this absence of pneumonia has been partly accidental, since pneumonia after operation may be due to causes other than the anesthetic. The record is, however, striking, and all the more so because we have anesthetized without hesitation, in cases of pulmonary tuberculosis, bronchitis and empyema. It contrasts markedly with the record after open ether. Here in a series of 400 cases we have had one death from ether pneumonia, and two deaths, one with autopsy, from acute pulmonary tuberculosis.[26] The latter patients were both operated on for tuberculous glands of the neck. Both patients died rather late — in from two to three weeks — after operation,

25. Henderson: Shock After Laparotomy, Its Prevention, Production and Relief, Am. Jour. Physiol., 1909. xxi, 60.
26. Walsh: Chloroform Rather Than Ether Anesthesia in Tuberculosis, The Journal A. M. A., Aug. 28, 1909.

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but they ran a high temperature from the first. It was the opinion of Dr. L. V. Hammond, who has charge of the work on tuberculosis at the Johns Hopkins Hospital, that the etherization had lighted up small apical foci of disease undetected before operation.

In closing I do not wish to leave the impression that this form of anesthesia is free from danger. It is without danger so far as postoperative effects are concerned. During the administration, however, there are dangers, though these can always be prevented by careful and skilful administration, and arise from causes which can generally be foreseen. The method should not be used except by those who have made a special study of its problems.

SUMMARY

1. Rebreathing, when properly regulated and when the oxygen supply is ample, is harmless and can be put to a valuable use.

2. If we can prevent anoxemia, overconcentration of vapor and too great a depth of anesthesia, we can obviate most of the serious objections to the closed method of giving ether.

3. The process of rebreathing prevents the elimination of ether and chloroform by way of the lungs, and overventilation of the lungs hastens the elimination.

4. It is suggested that after any administration of ether or chloroform, overventilation of the lungs be brought about by the use of mixtures of oxygen and carbon dioxid.

5. Morphin, or any drug which depresses the respiration, retards the elimination of ether or chloroform.

6. A method of administering nitrous oxid and if necessary ether with oxygen by the method of rebreathing is described and its advantages and dangers discussed.

Its chief advantages are (1) the rapidity and pleasantness with which anesthesia is established; (2) the ease with which any depth of anesthesia can be secured; (3)

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the prevention, to a very large extent, of postanesthetic vomiting, pulmonary complications and abdominal distention.

Its chief dangers are (1) anoxemia due to a failure to give sufficient oxygen or to an obstructed air-way; (2) impediments to the respiration, which in a long anesthesia may exhaust the patient; (3) with cardiac cases excitement during the period of induction.

ABSTRACT OF DISCUSSION

Dr. Yandell Henderson, New Haven, Conn.: It seems to me dangerous to have a man breathe for any length of time through a long tube in that way. Too much stress is laid on various fixtures; there seems to be too much ventilation. We used to think we should give the patient plenty of oxygen; this apparatus is designed to keep carbon dioxid in. We already have a tube, the trachea. A man told me this morning of a case in which the trachea and blood-vessels were cut and as soon as he sewed up the trachea the man began to breathe normally. That shows that in order to keep a man breathing vigorously he must breathe through a tube, and Nature provides it. When a man breathes through his mouth he gets more ventilation than when he breathes through his nose. Carbon dioxid is a diffusible gas; if the skin is off and there is congestion and disturbed vascular conditions it is because of the absence of carbon dioxid; if carbon dioxid is put over the surface these changes do not occur. We do not draw fresh air into our lungs. It would be the simplest matter in the world for Nature to have devised a mammal as a long breathing animal in which the lungs collapsed every time; it would be a simple matter for the thorax to go down until the lungs collapsed completely; then when we took a respiration we would draw fresh air in. But it does not work that way; to a large extent it is an effort to prevent carbon dioxid from getting out rather than to get oxygen in.

Dr. J. F. Hultgen, Chicago: The case Dr. Henderson referred to came to me accidentally. There being no surgeon around, no one but interns, I had to sew up the man's trachea, which he had cut with suicidal intent. He was fainting from lack of blood when he came to the hospital. The man coughed and sputtered around on the table and so we anesthetized him through the tracheal opening. His breathing was very shallow, and I had an intern stand with a stethoscope to hear if the heart was beating (it had been suggested that we let the man alone, as he would die anyway). I put in two or three sutures on either side, not touching the cartilage, and as soon as I had these sutures in I had the intern tighten them, he

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holding them on one side and I doing the same on the other side, thus approximating the two ends of the trachea. As soon as we did this, the up and down movements of the chest became very extensive—more so than normal. It seemed to me this might be made use of in a great deal of thoracic work and lung surgery; that artificial tracheotomy of this sort might be advantageous. This was such a remarkable case that the nurses and those around were called to witness it. The author has brought up an interesting point about anesthesia. When I was an intern we used to give the anesthetic with a cone; we had the patient sleep for hours with this cone, pouring in a dram or two of ether at a time. The carbon dioxid theory of Dr. Gatch I think offers a good interpretation for this.

Dr. W. D. Gatch, Baltimore: I do not oppose the use of the old-fashioned etherizing cone. It can probably be used so as to meet the physiologic requirements more nearly than an open mask.

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VERRUCA PERUANA

S. T. DARLING, M.D.
ANCON, CANAL ZONE

One of the most interesting diseases in South America is the one known as "verruca peruana" (*Verruga peruviana*), *fiebre de la Oroya,* or "Carrion's fever," as it is called in Peru, in honor of Daniel Carrion, a young Peruvian who died as a result of his zealous attempt to determine the infectious nature of the malady which, although given the common-place appellation of "wart," is a very serious and frequently fatal disorder.

Some knowledge of the disease is necessary to Americans, from the fact that American physicians have from time to time passed through the endemic region or have engaged in professional work in connection with some of the American commercial interests in Peru.

The disease is interesting from several points of view: to the parasitologist on account of the peculiar bodies in the erythrocytes, and on account of its probable transmission by ticks or other suctorial invertebrates having a peculiar geographic and altitudinal distribution; to the hematologist, on account of the remarkable blood-picture in the malignant form of the disease, there being a profound anemia; to the physician and quarantine officer, from the fact that the disease is rife in certain districts in Peru, where Americans have commercial interests and where American physicians and engineers, bridge-builders and other mechanics have occasion to pass through or work within infected zones. Convalescents occasionally return to the United States with some evidences of the disease still present on their persons.

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It is of additional interest to Californians because one of the very few accounts of the disease by Americans is that of Browne.[1]

GEOGRAPHICAL DISTRIBUTION

Verruca peruana is an infectious disease in which a fever of irregular type, associated with more or less severe anemia, is followed by a wart-like eruption of the skin, and sometimes of the mucous or serous membrane.

Formerly, it is believed, the disease had a much wider distribution than it has to-day. It is now encountered in certain narrow valleys on the western slopes of the Peruvian Andes, between latitudes 8 and 13° South, and at altitudes of from 1,000 to 12,000 feet. It is distributed along narrow tributaries which drain into rivers flowing into the Pacific. The disease is never contracted in the lower coastal plain, but always up in the valleys at the higher altitudes mentioned, not less than 28 to 60 kilometers (16 and 36 English miles) from the sea. Neither does it cross the divide, for it is unknown on the eastern face of the Andes. It is encountered oftenest at altitudes of from 2,000 to 6,000 feet.

The chief endemic areas are to be found in the departments of Ancachs in the Province of Huarez; and in S. Bartolomé, Casapalca, Chosica, and Santa Eulalia in the Department of Lima.

The mortality from verruca was so great during the construction of the Oroya Railroad, which extends from Lima to the Cerro de Pasco mines, that one of the large bridges crossing the river is known generally as "Verruca Bridge."

Peruvian physicians believe that only by sleeping in an infected district or by passing through it at night can the disease be contracted; and it is generally believed that the disease is transmitted by the bite of an insect. This naturally suggests a carrier in the shape of a tick

1. Browne: Verrugas and Arroyas Fevers, Tr. Med. Soc. Cal., 1872-1873, p. 173.

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or mosquito, or other suctorial invertebrate having a peculiar altitudinal distribution.

CLASSIFICATION

Two forms of the disease are recognized: the malignant and benign.

Malignant Form.—This is known as "Oroya fever," "Carrion's fever" or *fiebre grave verrugas.* The initial stage of this form corresponds with that usually noted in severe acute infections. The second stage constantly exhibits fever of an irregular remittent or intermittent type. There is a rapidly progressive and severe anemia, the erythrocytes falling below 1,000,000, sometimes even to 500,000 per 1 c.mm. There is poikilocytosis, polychromatophilia, enormous numbers of nucleated red cells, leukocytosis and high color index. Coincident with the anemia there is vertigo, great restlessness and air hunger. The sensorium is always clear and the mortality very high. The third or eruptive stage occurs in the small percentage of patients who recover from the *fiebre grave.*

Benign Form.—In this group Barton places the milder forms of verruca infections. They are quite common and the mortality is low. The symptoms are more undefined and the patients usually follow their vocations. The anemia and fever are moderate, and the eruption is more frequenty of the nodular type and lasts longer than in the malignant forms.

The second stage is followed by the skin eruption which appears first as an exanthem of small, purplish-red spots, which become papular and later develop into warty excrescences occasionally of large size, having a tendency to spontaneous hemorrhage. The lesion may occur on the mucous or serous membranes and deep subcutaneous tissues. After lasting for from four to six months, the eruption disappears by involution or ulceration.

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The period of incubation, if we consider the experiment of Carrion, is about twenty-one days.

There is no natural immunity to the disease of any kind—race, age or sex. Scheube says that infants have been born with the disease on them.

DURATION

The duration of the disease varies considerably, being a couple of weeks in the *fiebre grave,* to months and years in the other forms. The mortality among natives is said to be 10 per cent.; among whites 40 per cent. In the Oroya fever, however, it is 85 per cent. to 90 per cent. Frequent complications are septicemia, exhaustion, anemia, infections by the typhoid colon group of bacilli and tuberculosis.

ETIOLOGY

Little can be gained by delving into the historical aspect of this subject. The infectious nature of the disease was demonstrated in 1885 by Daniel Carrion, a young Peruvian medical student, who inoculated himself in both arms with blood taken from warts. After a latent period of twenty-one days, he entered the febrile stage of the disease and died eighteen days afterward of *fiebre grave,* before the development of the eruption.

It is curious to note that in verruca several strains of paracolon bacilli have been isolated by Barton and Biffi, from patients suffering from *fiebre grave,* and also from cadavers in cases of the same disease; just as in yellow fever, varieties of paracolon bacilli, having been obtained from yellow fever patients before and after death, were thought by competent observers to be the cause of the disease.

In 1900, Barton called attention to the existence of infections by members of the typhoid-colon group of bacilli in patients suffering from verruca. These infections were noted during the course of an attack of verruca, particularly toward the end of the second stage, and during the eruptive process. Barton believes that

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the "typho-coli infections" alter the symptomatology of verruca and aggravate its progress to a considerable degree.

Biffi reports isolating two strains of bacilli, one resembling *B. paratyphosus,* Schot, the other, Gaertner's bacillus.

To those who have had any experience with infections by members of the typhoid-colon group in the tropics, and in view of our knowledge of the history of the relation of *B. icteroides* and bacillus *x,* of Sternberg to yellow fever; the relation of the hog cholera bacillus to true hog cholera which, as De Schweinitz and Dorset have shown, is due to a filterable virus; these bacteriologic findings of Barton and Biffi are very interesting, and they add another disease to the list of those frequently complicated by infections with bacilli of this group.

In October, 1905, Dr. A. L. Barton[2] of Lima called attention to certain bacillus-like elements in the erythrocytes of two patients suffering from *fiebre grave de verrugas.* Later, in January, 1909, he described the bodies found in fourteen additional cases. Barton stated his belief that the bodies were protozoa and were the specific agents of the disease. Gastiaburú and Rebagliati,[3] in October, 1909, confirmed Barton's findings.

Barton's views as to the relation of his intracellular *x*-bodies to verruca have not been generally accepted by European investigators; chiefly, I believe, for the reason that the latter have studied films in which the *x*-bodies were oftenest seen after they have "broken up," to use Barton's expression. In this condition they are more nearly like basophilic granulations. The illustrations by Galli-Vallerio[4] are entirely unlike the appearance of *x*-bodies when they first appear in the erythro-

2. Barton, A. L.: Descripcion de Elementos Endo-globulares hallados en los enfermos de fiebre verrucosa, Charon. Med. enero, 1909.

3. Gastiaburú and Rebagliati: Sobre la hematologia y etiologia de la Enfermedad de Carrion, Cronica Medica, Nov. 15, 1909.

4. Galli-Vallerio: Centralbl f. Bakteriol., I, ab. orig., lviii, 228.

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cytes in verruga. Those of Basset-Smith,[5] while much too coarse, approach more nearly in two instances to the exact morphology. The general impression received from Mayer's figures[6] is that of cell degeneration, the rod forms being relatively too small and not in such relatively great numbers as they are in the early stage of the disease or during a recrudescence.

The *x*-bodies of Barton appear in the blood in the "severe wart fever" and disappear about the time of the appearance of the eruption. They are always seen first as slender rod-like forms with rounded free ends. They are situated within the erythrocytes but, according to Barton, cannot be detected in the fresh blood; consequently their refractive index must coincide with that of the erythrocyte. They are stained best with Giemsa stain, but not quite so well with other stains of this class when stained by the ordinary methods. One or both ends may take the stain a little more deeply than the rest, or a deeply staining swollen dot may sometimes be seen between ends. The rods are occasionally single, though oftener two or more, up to six or eight, may be seen, frequently grouped in parallel series, or in such manner as suggests, according to Barton, a process of reproduction. This, however, may be otherwise interpreted, for I have frequently found that rods of melanin in malarial zygotes of infected mosquitoes have exactly the same grouping. Filaments or irregularly disposed branched or pseudo-branched forms are seen. The rods are generally slightly curved, and when the erythrocyte containing them is torn, while making the smear, the bodies can be seen to preserve their morphology and staining characters outside the cell. They stain a dark blue or purple; never faintly blue, with sharply differentiated chromatin substances. In this respect they differ from protozoa and give the impression of being more like spirochetes than any other known type of micro-

5. Basset-Smith: Brit. Med. Jour., Sept. 18, 1909.
6. Mayer: Centralbl. f. Bakteriol., I, ab. orig., lvi, 309.

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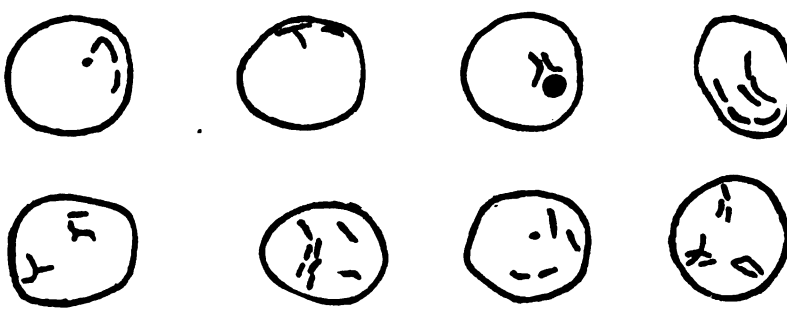
organism. After a few days they are seen to lose their slender rod-like shape and become more irregularly swollen, distorted and fragmented. At this time they usually take the stain more deeply.

When the disease progresses favorably, the bodies disappear and the eruption comes out. If the bodies are seen to reappear in their slender rod-like form, it can be noted at the same time that the patient's symptoms have become more grave, and if the thin rod-like elements continue in large numbers in the peripheral blood, the patient dies. In these instances nearly every erythrocyte is invaded.



Erythrocytes showing *x*-bodies in a fatal case of verruca peruana two days before death.

Barton states that the longest period the bodies have remained in the peripheral blood is twenty days.

If one examines blood of verruca patients after the *x*-bodies have undergone involution and become pyknotic and polymorphous, the impression of a peculiar basophilia of the erythrocytes would no doubt be entertained, but if one watches the rod-like forms from day to day in a malignant case during which there is a period of amelioration of symptoms followed by recrudescence of the disease, one is very strongly impressed with the opinion that the *x*-bodies represent microorganisms of some kind.

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According to Barton, the recovery of the patient coincides with the disappearance of x-bodies from the peripheral blood.

What is the nature of the x-bodies? 1. Are they some form of basophilia or degenerative change of the erythrocytes or are they nuclear remnants? 2. Are they localized spots of degeneration of the erythrocyte, surrounding and obscuring a very minute or ultramicroscopic microorganism? 3. Are they bacilliform *Babesia*? 4. Are they bacilliform bodies invading the erythrocyte, such as have been described by Laveran and Carini[7] in lizards? 5. Are they related to the endocorpuscular bodies described by Graham-Smith[8] in the red corpuscles of moles? 6. Are they some representative of the sporozoa?

Without going into a detailed discussion of this phase of the subject, I will merely state that the slender rod-like x-bodies seem to me to represent some unique type of microorganism, for there is nothing exactly like them in the annals of parasitology or hematology.

BLOOD CHANGES

In the malignant form of the disease very remarkable changes are noted. Briefly, the chief characters are basophilia of the red cells, the presence of many nucleated red cells, x-bodies in various stages, and numerous marrow-cells, all rapidly escaping from the marrow before they have reached the mature type seen in the peripheral blood during health.

The red cells show much basophilia, blue basophilic punctations and red nuclear remnants. There are crises in which enormous numbers of nucleated reds, chiefly normoblasts, are seen. There is much basophilic punctation of those nucleated reds which show a polymorphous or budding nucleus. Many microcytes and macrocytes are seen and there is some agglutination of the red cells.

7. Laveran and Carini: Ann. de l'Inst. Pasteur, xxiv, 152.
8. Graham-Smith: Jour. Hyg., Cambridge, v, 453.

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With regard to the leukocytes, there is a leukocytosis from time to time, with the appearance of marrow-cells of various types, such as myeloblasts, neutrophilic and mast myelocytes, transitional leukocytes, and polymorphonuclear leukocytes with bluish-green granules. There is a diminished number of eosinophils.

The blood-platelets are notably diminished in number and have lost to a considerable degree their power of agglutination.

REPORT OF AUTOPSY

Patient, A. L. O., male, aged about 25, native of Pennsylvania, U. S. A., bridge worker, contracted verruca while at work on the Oroya Railroad. During convalescence and while returning to the United States, he died on the steamer in Panama Bay, Sept. 18, 1908. The body was packed in ice and next morning, through the kindness of the chief quarantine officer, Surgeon J. C. Perry, U. S. P. H. and M. H. S., I had an opportunity to make a post-mortem examination of the body.

Sparsely scattered over the body, particularly about the ankles, were circular reddish-brown raised papules and some few pigmented spots of a dusky reddish-brown color. One of these latter in Scarpa's triangle in the left groin, 6 mm. in diameter, had broken down and contained necrotic material. These represent the "verrugas," some of which were still present, though of small size. Others had evidently undergone the process of involution mentioned above and a few had ulcerated.

There was generalized tuberculosis of the lungs, pleuræ, lymph-nodes, spleen, kidneys, and liver, internal hydrocephalus, hydroperitoneum and hydrothorax. The femur marrow was not definitely hyperplastic.

Smears from the spleen contained a little melanin, not positively malarial. No malarial plasmodia were detected. Smears from other viscera showed no ϖ-bodies, save those from the rib-marrow which contained a few rod-like bodies, not definitely in the erythrocytes.

Microscopic Examination.—Skin. The epithelium was flattened out and the papillæ had disappeared. The lymph-spaces of the corium were filled with large, phagocytic cells, distended with reddish-yellow refractile granules of different sizes, evidently red blood-cells in various stages of decline. The deeper connective tissue, particularly around the sweat-glands, was infiltrated by round-cells, and cells of the connective tissue

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type. In this section the arterioles were not at all distended, numerous nor conspicuous, and this area evidently represented a small verruca which had undergone involution.

Another section of skin showed the epithelium thrown into folds without atrophy or obliteration of the papillæ. Deep in the subcutaneous tissue there was a large area of necrosis containing fragmented nuclei and eosin staining débris. On the margins of this area there were numerous giant cells with mural nuclei, epithelioid and plasma-like cells and still more peripherally a number of round cells; but interspersed with these proliferated cells were many arterioles and capillaries with thin attenuated walls, with their lumens stuffed with red blood-cells. In some instances an arteriole might be seen immediately beside a giant cell. The section was very vascular and represented a tuberculous process, superimposed on a vascular verruca.

The kidney, spleen and lymph-nodes showed nothing of note but disseminated tuberculosis.

In the striated muscle a number of the fibers were swollen, the cross-striations obliterated, and represented a hyaline change.

These meager notes from the autopsy and from the examination of tissue are of interest, for they suggest very strongly that the acid-fast bacilli in verruca tissue described by various writers are really tubercle bacilli, and that those who have merely examined tissue without seeing the autopsy, and who have described necroses in verruca tissue, which very closely resemble those of tuberculosis, have been describing tuberculosis of various viscera which has existed as a complication of verruca and which do not represent any specific change due to verruca *per se*.

PROPHYLAXIS

As the disease is limited to certain endemic regions, and is generally contracted at night, it may be prevented, of course, by keeping out of the danger zone. During 1909 an American bridge company undertook the construction of several bridges on the Oroya Railroad. The engineers and workmen engaged in putting up the first of these structures encamped within a verruca zone, and suffered much from the disease. At the

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suggestion of Dr. Barton, it was arranged that the men should sleep in a place a few kilometers distant, out of the endemic district, while they continued their work in the day time as usual. From that date there were no new cases. Peruvian physicians are quite alive to the economic importance of this disease and we may expect them to determine in due time the mode of infection, the true pathogenic agent, and thus establish a means of preventing the ravages of this tropical scourge.

In conclusion it should be stated that whatever the final opinion with regard to the *x*-bodies may be, the disease in all its aspects will amply repay careful study and research into the mode of transmission, relation of the *x*-bodies to the different clinical phases of the disease, the pathology and treatment.

I am under special obligations to Dr. A. L. Barton of Lima, Peru, for his kindness in furnishing me with clinical notes and consecutive blood-films from several cases of verruca.

Ancon Hospital.

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THE WHITE CELLS IN TUBERCULOSIS

W. WARNER WATKINS, M.D.
PHOENIX, ARIZ.

Study of the leukocytes in their relation to disease, or to a particular disease, soon impresses one with the truth of Professor Ehrlich's statement[1] that the biologic variations of the white cells make them the most interesting study in pathology. Could we definitely know what the changes of the leukocytes are, at the onset and during the course of a disease, we would have an invalable aid to the diagnosis and prognosis of that condition. Study of immunity and of the broad field of biologic adaptation in its application to pathology has revealed the white cells as the mobile tissue of the body, the elements most quickly adapting themselves to changes in environment by undergoing endless variations in the presence of stimuli furnished by pathologic organisms and their toxins. Unfortunately, however, for clinical and therapeutic purposes, these variations are, as a rule, so similar in different diseases and so inconstant in the same infection in different individuals that their diagnostic and prognostic value becomes somewhat uncertain.

So far as tuberculosis is concerned, the white cells have been the subject of but limited study, which is rather strange since the reaction of the leukocytes in this wide-spread condition is exceedingly interesting and ought to become a sound basis for practical therapeutics. In America the work of Webb[2] is the most valuable contribution to investigation along this line.

1. Ehrlich: Anemia.
2. Webb: Hematologic Studies in Tuberculosis.

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For the sake of clearness this paper outlines its matter under three divisions:

1. The most important known facts regarding the white cells in tuberculosis.

2. The conclusions growing out of limited and incomplete personal observations.

3. The lines along which further investigation seems to be most needed.

I.—THE MOST IMPORTANT FACTS CONCERNING THE WHITE CELLS IN TUBERCULOSIS

The biologic law that the nucleus is the dynamic center of living cells and that the cytoplasm is only a means of communication between this center and the surrounding medium, holds true for leukocytes. Then one would naturally conclude that of all the white cells the most powerful ones are those with the largest and most perfect nuclei; this conclusion is justified by the work of several investigators who have proven that the most resistant and, consequently, the most powerful white blood-cells are the large and small lymphocytes. It is interesting, also, in this connection, to note that Ehrlich's assertion that the lymphocytes do not possess ameboid movement and do not respond by chemotaxis to stimuli, has been vigorously disputed by several writers.

In resisting a tuberculous infection it has long been known that the lymphocyte is the cell particularly effective against this bacillus. The term "lymphocyte," as used herein, classes under that word, without any attempt at differentiation, both the small mononuclear leukocyte (the lymphocyte of Ehrlich or small lymphocyte of American writers) and the large mononuclear leukocyte (the large lymphocyte of American writers), since no one has yet made any distinction in their function. That these cells are attracted particularly by the tubercle bacilli is doubtful, their effectiveness against these organisms being largely explained through the work of Bergel, confirmed by Webb and his assistants,

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that only lymphocytes have the ability to dissolve the waxy sheath enclosing tubercle bacilli and protecting them against the destructive antibodies of the serum and against ordinary phagocytes. It is the universal observation of hematologists that there is an increase in the lymphocytes in tuberculosis, but the conclusion heretofore drawn, that this lymphocytosis is due to secondary anemia resulting from the disease, is erroneous, for this increase in mononuclear cells occurs only during the process of recovery from, or successful resistance of, tuberculosis, and does not occur when the disease is progressing unfavorably. A fact which simplifies routine observation in this connection is that where there is an increase in the mononuclears (except in lymphatic leukemia, where all the elements are increased), this change in percentage is due to an actual relative increase and is not accompanied by a rise in the total leukocyte count.

II. CONCLUSIONS DRAWN FROM PERSONAL OBSERVATIONS

Personal observations have been made from 112 blood-counts in 100 individuals, with results as follows: Twenty-two healthy adults gave an average lymphocyte count of 41.5 per cent., ranging from 29 per cent. to 57.5 per cent. Thirteen patients definitely cured of tuberculosis of the lungs gave an average lymphocyte count of 45 per cent., ranging from 35 per cent. to 67 per cent. Twenty-four counts on patients with tuberculosis checked or healing gave an average percentage of 38, ranging from 30 per cent. to 50 per cent. Forty-four counts from patients in whom the disease was gradually or rapidly progressing gave an average of 25 per cent., ranging from 10 per cent. to 35 per cent. Six who were not seen after the original examination, but whose cases were all advanced, gave an average count of 24 per cent. Two adults presenting themselves as normals, but whose appearances were suspicious, gave counts of 19 per cent. and 20 per cent. The conclusions based on these observations, in view of the estab-

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lished facts concerning lymphocytes in tuberculosis, together with the work of contemporaneous and accurate observers, are as follows:

1. These observations agree entirely with those of Webb that the percentage of lymphocytes affords an apparently reliable indication of individual resistance to tuberculous infection. A broad classification of patients in whom tuberculosis is still active obscures the important fact—invariably observed in a close analysis of individual patients—that the percentage of lymphocytes corresponds closely to the condition of the patient and the progress of the disease.

2. There is present in many healthy individuals a considerable increase in the percentage of lymphocytes, so that instead of being 30 per cent., they approximate 40, 45 or 50 per cent., or more. These increases are observed particularly in high altitudes and in lowlands where the atmosphere is rarefied by absence of moisture and by high temperature. The conclusion is certainly justified, that an individual presenting such an increase in number of those defensive cells known to be most effective against tubercle bacilli, presents, likewise, an increased resistance against infection by those organisms.

3. There exists in human beings who have definitely recovered from tuberculosis, a permanent increase in the percentage of lymphocytes, the counts ranging from 40 to 70 per cent. That such an increase in those cells known to be particularly destructive to tubercle bacilli affords a relative immunity to infection by those organisms, is a natural conclusion. This is a definite biologic confirmation of the much-disputed statement that cured tuberculosis produces immunity — the degree of the immunity being limited only by the definiteness of the recovery.

4. In patients with active tuberculosis, there occurs coincident with, or preceding, the checking of that activity, an increase in the percentage—i. e., the number—

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of lymphocytes, which continues as long as the lung tissue maintains its resistance and remains permanent if this resistance proceeds to eradication of the tuberculous area. This lymphocytosis is so definite and unfailing that it offers the most dependable means that we now have of foretelling from week to week and from month to month what the future course of the disease in those patients will be.

5. On the other hand, preceding by a variable time the lessening of resistance and consequent invasion of new tissue by the bacilli, there occurs a decrease in the percentage—i. e., the number—of lymphocytes. This decrease can be observed before any appreciable change in the lungs can be detected, and offers an even more definite and reliable indication of the probable course of the infection in those cases which are so disconcerting in their failure to observe prognoses.

6. The blood of tuberculous patients with lymphocytosis presents, usually, an interesting picture and one very different from that of normal blood. Lymphocytosis is said to depend chiefly on an increase of Ehrlich's large mononuclears—those cells reputed to originate in the bone-marrow. This is true, though these newly formed cells differ in appearance from the ordinary large ovoid lymphocyte. The small lymphocyte, forming, ordinarily, about 25 per cent. of the total white cells is, occasionally, the cell which multiplies; but, as a rule, this type of cell becomes subordinate and the mononuclear cells which appear in the blood so rapidly during a tuberculosis in the process of healing may be two or three times as large as a polynuclear, and have a large, irregular cytoplasm and a very large, sometimes irregular, nucleus.

7. Actual count of the white cells has not been made in these observations, because the necessity for it was not evident, although, in order to avoid criticism, this should, perhaps, be done. In uncomplicated tuberculosis there is known to be no leukocytosis, so that an

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increase in the percentage of one type of cell as shown on a smear preparation, is an actual increase in number of that type. The criticism that a mixed infection with pyogenic organisms will bring about an increase in the number of polynuclears and, consequently, a decrease in the percentage of mononuclears without an actual decrease in their number, is a criticism of scientific accuracy which will have to be answered by checking such investigations against actual counts of the leukocytes. The clinical fact remains unaltered, however, that the percentage of lymphocytes is an exact and reliable indication of the course which a tuberculous process will assume in the immediate future—whether this percentage is an actual change in number in cases of tuberculosis uncomplicated with pus organisms, or whether it is an apparent change owing to the preponderance of polynuclears in mixed infections.

III. LINES ALONG WHICH FURTHER INVESTIGATION IS NEEDED

In viewing the lines along which further investigation is needed, the field is seen to open up with every new step and only a few suggestions are offered.

1. The conclusions offered above need to be confirmed by continued investigation, controlled by actual counts of the white cells.

2. Healthy individuals in different sections of the country should be examined in large numbers to determine, as Webb has been doing, in what sections of the continent there is a tendency to an increase in those cells which most effectively resist tuberculosis.

3. The particular methods by which individual resistance against tuberculosis can be raised should be ascertained, with the lymphocyte percentage as an accurate guide to the degree of such a resistance. In the great campaign against the white plague, prophylaxis must eventually be the means of eradicating it, and when such methods of increasing individual resistance are definitely

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known they can be utilized in prophylactic treatment, whether they are dependent on climate, gymnastics, or specific immunization.

4. The relationship between the reaction of these cells and the administration of specific agents like tuberculin, vaccines, immune serums, etc., should be determined; also to what extent the changes in the lymphocyte percentage can be utilized as a guide in specific treatment. One writer makes the statement that the lymphocytes increase after an injection of tuberculin. If the effect of tuberculin is to stimulate those cells which have the ability to destroy tubercle bacilli, there must be a close connection between that effect and the increase in lymphocytes. If the effect of tuberculin and allied remedies is to cause the production of antibodies in the blood-serum, lymphocytes being known to participate in the production of such bodies, it is evident that there are relations of cause and effect not yet discovered.

5. The trend of study and investigation in tuberculosis is toward the blood—blood-serum and blood-cells—and the more these are studied, the clearer is the conviction the world over, that Koch, in his discovery of the bacillus and of tuberculin, did not, by any means reach the summit of valuable knowledge in this disease.

23 East Adams Street.

ABSTRACT OF DISCUSSION

Dr. Gerald B. Webb, Colorado Springs: Dr. Watkins' excellent paper corroborates our former work. When we discovered the increase of lymphocytes in Colorado Springs we considered it due to the same marrow hyperplasia which causes the increase of the red corpuscles. Professor Zuntz has recently written me that he considers these changes due most probably to lack of oxygen in the bone marrow. We have been able to produce the same results by hyperemia of the marrow, increasing the lymphocytes by 100 per cent.

Dr. Watkins spoke of the differential blood-counts found at the Salton Sea. I would like to ask our Chairman (Dr. Henderson) if he could explain the possible hyperplasia of the marrow in this region by reason of stimulation due to excess of carbon dioxid retained in the blood.

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Dr. Yandell Henderson, New Haven, Conn.: I confess that I cannot give any explanation of the effect of the Salton Sea. There have been extensive investigations recently in Germany on the effects of sea baths and seashore climates, but so far as I am acquainted with them they do not offer any ground for an answer to the question.

Dr. J. E. Pottenger, Monrovia, Cal.: The attempt to determine the variation in leukocytes at different altitudes is a good one, as no doubt there is considerable physiologic variation. My work has been done at an elevation of 1,000 feet. I have made about 800 differential counts on some 600 patients. I have not been sufficiently impressed with any particular variation from the normal in lymphocyte percentage to attempt to establish a rule, aside from the increased percentage in the early stages of the disease and a decrease, often, in serious cases. From the data presented by Dr. Watkins the question naturally arises as to what the value of altitude might be in establishing immunity. Sufficient work has already been done to show that the lymphocyte is probably more active in increasing the resistance of the individual in tuberculous disease than we had formerly supposed, but since this same increase in lymphocytes is to be seen in normal people at an altitude, we are obliged to consider that such increase in diseased persons must be in part physiologic and cannot be considered as a favorable reaction against the disease process.

As the technic employed in making counts is very important, I wish to ask Dr. Watkins what technic was employed in making his computations.

Dr. W. W. Watkins, Phoenix, Ariz.: I will say, first, that my chief object in presenting this paper was that I thought the criticisms which would be offered would be of value to me in future work along the same line. As to the criticism regarding conclusions based on only 100 patients, of course, conclusions of value cannot be drawn from 100 examinations, in any condition, if that were all; but as there were thousands of cases reported in literature, I felt justified in drawing conclusions which simply confirmed the work of other men.

As to the technic of the smears, I used both the method recommended by Ehrlich with cover slips and the method recommended by DaCosta with slides. The one I chiefly used is that of taking the ordinary slide, properly cleaned and prepared, putting on the drop of blood, bringing the end of another slide up to the drop and then pulling it away, the blood following the slide. In these smears, the drop was kept in the central portion of the slide. I take three or four, never less than two. The smears, when the leukocytes are bunched at the terminus of the smear, cannot be depended on. The leukocytes must be distributed evenly throughout the smear to be of value. The stain used was Wright's.

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THE PATHOGENESIS OF THE BALANTIDIUM COLI *

FRED B. BOWMAN, M.B. (Tor.)
BALTIMORE

During the past decade the *Balantidium coli* has been attracting much attention in respect both to its pathogenicity and to its life history.

In Manila the material for study, both clinical and pathologic, has been comparatively abundant. The literature on the subject has been thoroughly reviewed by previous writers and will not be discussed here. Only those points bearing directly on the pathogenicity of the organism will be considered. During the past three years I have examined many specimens containing the organism, but have been unable to follow many of the cases because the patients complained of no symptoms and could not be detained in the hospital; in all I have been able to study clinically ten cases, three of which came to autopsy and have been reported elsewhere.[1]

At present, four cases are under observation, three of which have balantidia in the feces intermittently, the other one, although complaining of little diarrhea, has them constantly present.

ZOOLOGY

Balantidium coli belongs to the *infusoria* class; subclass, *Ciliata;* order, *Heterotrichida;* family, *Bursaridæ.*

It has an oval body from 0.07 to 0.1 mm. in length by 0.05 to 0.07 in width, is pointed anteriorly when the

* From the Biological Laboratory of the Bureau of Science, Manila, P I.

1. Philippine Jour. Sc., December, 1909, iv, No. 6; April, 1911, vi, No. 2.

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periostome is extended and covered with parallel rows of cilia giving it a striated appearance. It has a bean-shaped macronucleus and a globular micronucleus. It apparently has three methods of reproduction: budding, conjugation and division, though in my studies I have only been able to see definitely the latter, and this is probably the most common. The organism may change its shape in passing through some obstruction, narrowing until the projected portion appears almost like a pseudopod. Sections cut through tissue very often show these processes and they might be mistaken for budding forms.

In the fresh feces, organisms are found in pairs and even larger groups and this has probably often been construed as conjugation, but this grouping seems to be a characteristic of all ciliata and flagellata and is probably in most instances purely physical in character. Both in stained feces and in stained sections of intestinal ulcers these groups were seen, but no cytoplastic changes were found in the nuclei.

The rapid circular motion of the periostome cilia seems to exert an attraction which brings the organisms in contact. I have observed many times in fresh feces, two of them moving along rapidly in the fecal material, suddenly, on approaching each other, dart together and remain in this position for a considerable period of time, though no interchange of material could be seen taking place between them and no evidence of reproduction changes.

The hog has been thought to be the most common host of the organism, but the method of transmission to the human host is indefinite. In studying the organism in the human, I have never seen any evidences of encystment, though if man is infected from the hog, it is probably by resistant encysted forms.

Geographically the disease is generally distributed, cases having been reported from Russia, Sweden, Finland, Italy, Germany, Africa, China, North America and

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the Philippines and thus, it is in no sense distinctly tropical.

CLINICAL SYMPTOMS

These somewhat resemble those seen in amebic infections. First of all, mild intermittent diarrhea, each succeeding attack becoming more severe than the preceding one, and the simple diarrheic stool gradually becoming dysenteric in character. The patient complains of loss of appetite, indigestion, flatulence and pain in the lower abdomen. He may have palpitation. As the diarrhea becomes more severe there is some tenesmus, and bloody flakes and mucus are noticed in the feces. These symptoms may suddenly disappear without any treatment, only to return in perhaps a week or even a month, suddenly and with more severity. These attacks become more numerous and the patient becomes weak and emaciated. The stool finally consists of only necrotic material, clots of blood and mucus and the patient may die of exhaustion or as the result of perforation.

During the attack of diarrhea in the first stages of the disease, balantidia are found in the feces and are usually absent during the periods between the attacks. As the diarrhea becomes less intermittent, the organisms may be found at any time in numbers depending more or less on the character of the stool. They are sometimes found practically swarming in the mucous portions.

There may, or may not, be leukocytosis, my cases showing practically no increase in the number of leukocytes. A marked eosinophilia has been noted by many observers and I have also noted this fact, but the presence of intestinal worms in most natives in the tropics probably influences the blood picture to a great extent.

DIAGNOSIS AND PROGNOSIS

The diagnosis is made entirely on the finding of the organism in the feces and the absence of other intestinal protozoa.

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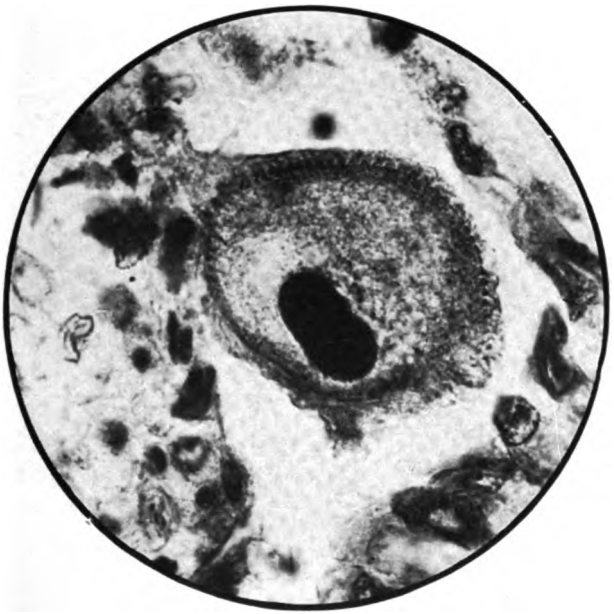

Fig. 1.—*Balantidium coli* in lymphatic gland.

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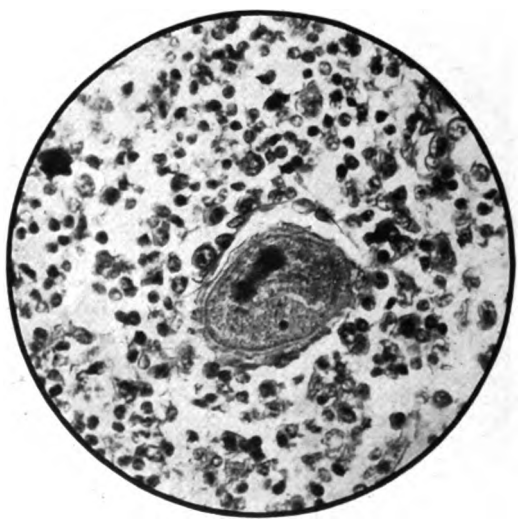

Fig. 2.—*Balantidium coli* in lymphatic gland, showing beginning nuclear division.

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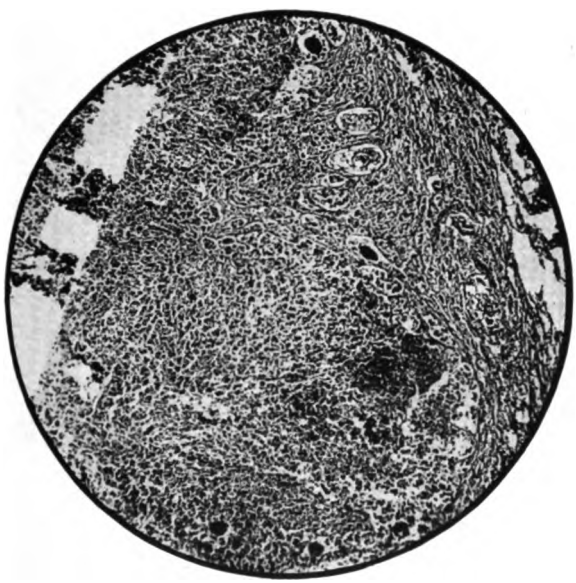

Fig. 3.—Numerous balantidia in lymphatic gland.

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Fig. 4.—*Balantidium coli* passing through basement membrane of a gland of Lieberkühn. This might be mistaken for a budding form. (Illustration from Strong's article, Pub. Philippine Isl. Bur. Sc. Biol. Lab., 1904, No. 24, p. 1.)

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Fig. 5.—Balantidia in a blood-vessel

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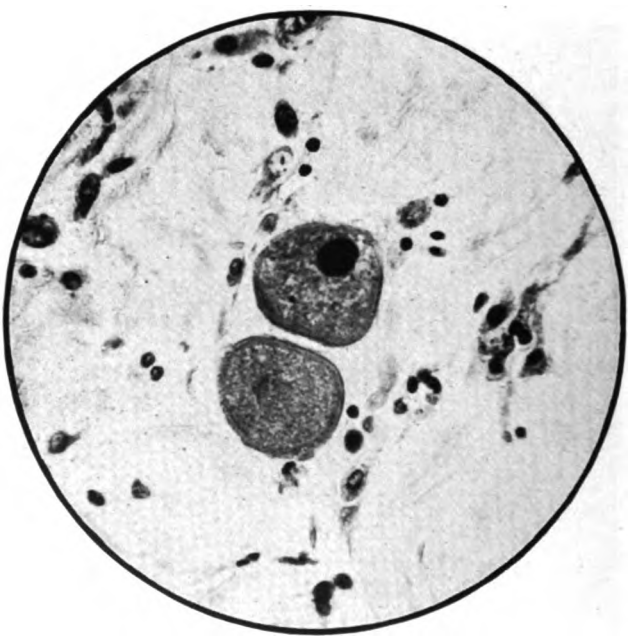

Fig. 6.—Two organisms in submucosa causing practically no cell reaction.

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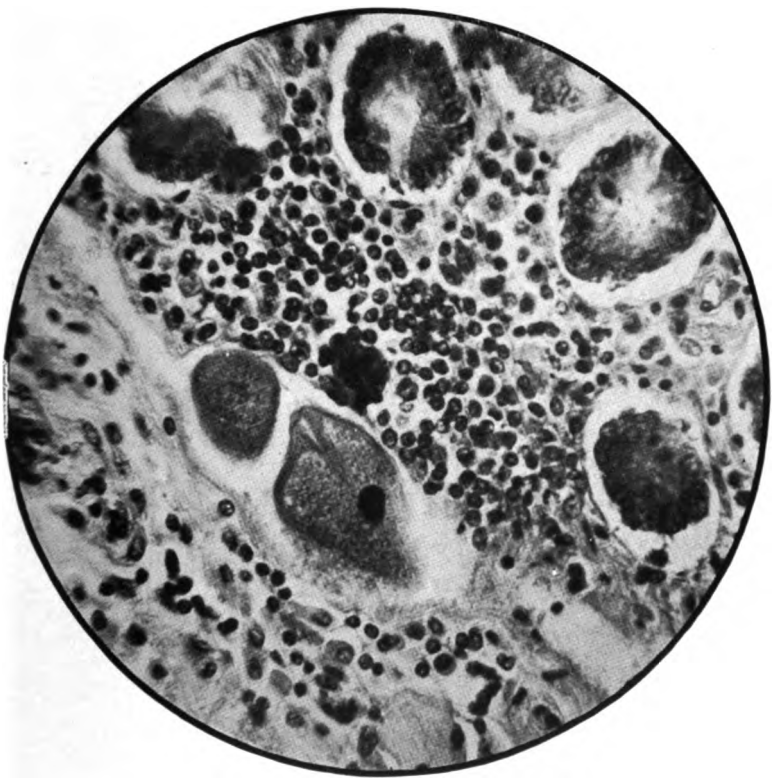

Fig. 7.—Two balantidia lying just beneath the mucosa. Numerous round cells may be seen, with evidence of beginning ulceration.

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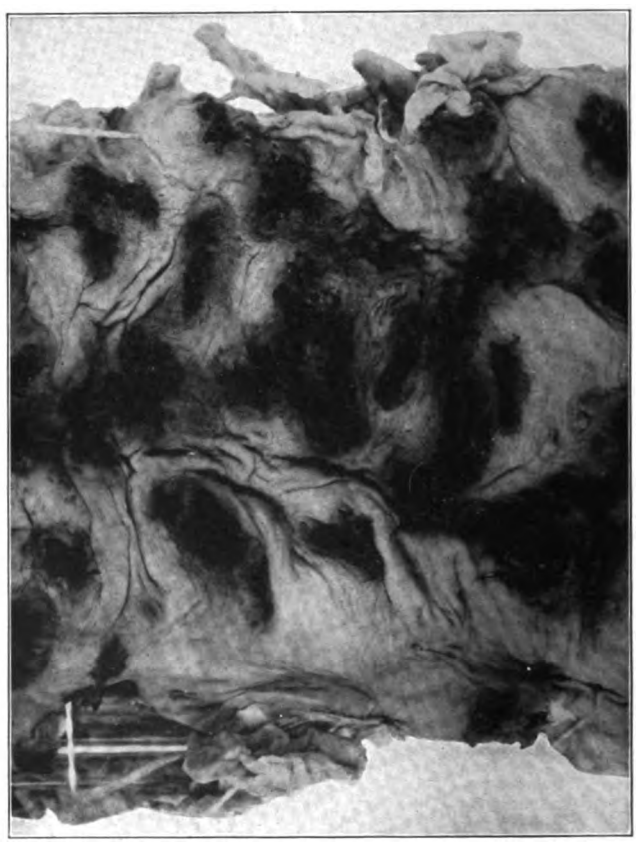

Fig. 8.—Ulceration of colon caused by *Balantidium coli*.

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Prognosis is not good even in the very early stages of the disease. As the infection progresses, it becomes rapidly worse and in the later stages, when the stool is distinctly dysenteric in character, the prognosis may be pronounced in most cases hopeless.

GROSS PATHOLOGY

In my cases the ulceration caused by this parasite has been limited almost entirely to the colon and rectum. In one case only, a few shallow ulcers were found a few centimeters above the cecum and in most, if not all, of the cases in the literature, the small intestine has been unaffected. The cecum may be greatly thickened where the most severe and chronic ulceration is present. In two of my cases, in some places it was as much as 3 cm. in thickness, and the rectum and part of the colon were a mass of ulcerating necrotic tissue.

The ulcers vary in size from 0.5 cm. to 3 or 4 cm. in diameter. They bear no distinct relation to the mesenteric attachment. The early ones are shallow, not injected at the edges and are not undermined. From the larger and older ulcers hang tags of black necrotic tissue and the edges are undermined, indurated and injected. The base may be thin, only the serosa intervening between the bowel lumen and the peritoneal cavity. In one of my cases, perforation had taken place in one of the ulcers of the cecum.

There is nothing to distinguish the late ulcerations caused by amebas from those caused by the *Balantidium coli,* though the early amebic ulcers appear to be sometimes more punctate in character.

The mesenteric lymph-glands may be enlarged and necrotic.

HISTOLOGIC EXAMINATIONS

The parasites are found in all the layers: mucous, submucous and muscular. They seem to be much more numerous in the submucosa than elsewhere, and in the blood-vessels, "nests" of them with twenty or thirty

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organisms massed together may be found. Some of them are found in the glands of Lieberkühn, and Strong has demonstrated a parasite rupturing the basement membrane and passing through the gland-wall. Where many of them are gathered together in the subglandular tissue, a surrounding zone consisting of plasma-cells and lymphocytes is found, with an abnormal number of eosinophils, but with very few polymorphonuclear leukocytes present. On the other hand, the cellular constituents of the necrotic material covering the ulcer consist largely of polymorphonuclear leukocytes. This fact would seem to indicate that the parasite, on first entering the tissue, causes a low-grade inflammation independent of any bacteria which it may have carried with it. The intestinal bacteria are the terminal invaders and cause necrosis of the tissue already undermined and weakened by the balantidia. Undoubtedly, many of the primary ulcers are caused by organisms entering the glandular layer, but, having once entered, ulceration may be the result of another process. On studying sections quite remote from any ulceration and through apparently uninjured mucosa, the organism may be found invading the submucosa and muscular strata, while in the mucous layer none are found. Where they are found singly, there may be no evidence of inflammatory reaction, but, in other areas where several of them are gathered together, there may be many round cells forming a surrounding zone, and in still other situations marked evidence of inflammatory reaction. In a study of many sections, all stages in this inflammatory process may be seen. From the single balantidium which seemingly has pushed itself mechanically through the tissue with little cell reaction, to groups of the parasites with surrounding zones of lymphocytes and plasma-cells which have infiltrated the mucosa itself, demonstrating a reaction which, with the invasion of intestinal bacteria, will terminate in ulceration.

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The organisms may enter the mesenteric lymph-glands and cause necrosis. In one of my cases, they were found very numerous in one of the sectioned glands and there was some increase in the polymorphonuclear elements present, but no bacteria could be demonstrated and there was no evidence of tuberculosis. If the organism can invade the mesenteric lymph-glands, invasion of the lungs and liver would seem much more probable.

In two of my cases, the marked adhesive pleuritis and pericarditis was very striking and, in view of the fact that there was no evidence of tuberculosis, the *Balantidium coli* may have been the primary invader causing these conditions, though sections from the diseased pleura and pericardium failed to show any organisms present.

ANIMAL EXPERIMENTS

In view of the fact that an epidemic of dysentery due to *Balantidium coli* in orang-outangs had been reported by Brooks,[2] and Noc[3] had reported a natural infection in a monkey (*Macacus cynomolgus*), it was decided to attempt to infect monkeys.

Feces containing many organisms from a case of balantidium infections were injected into the rectum of a monkey (*Macacus cynomolgus*) on several occasions, but the stool always remained negative and no symptoms of dysentery developed. This was done many times with different monkeys, always with negative results.

A colotomy was performed on another monkey and 20 c.c. of infected feces injected on two occasions. but the stool examinations always remained negative.

A section of a colonic ulcer from one of my cases was securely sutured in the wall of the colon of a monkey, in the hope that resting or encysted forms might be present which would be more resistant to manipulation incidental to the changing of the host. No infection of the animal occurred. As to cultivation, in this laboratory

2. Brooks: New York University Bull. Med. Sc., 1902.
3. Noc.: Compt. rend. Soc. de biol., 1910, lxiv, 878.

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we have been unsuccessful. I have observed the organism alive for twenty-four hours on Musgrave and Clegg's media, and Walker (in this laboratory) has noted life for six days, but with no reproduction, those alive being some of the individuals originally inoculated on the media.

SUMMARY AND CONCLUSIONS

Whether a break or abrasion in the mucosa of the intestine is necessary for the entrance of the *Balantidium coli,* whether it can force its way through the lining membrane by purely mechanical means or whether a cytolytic ferment is liberated, we do not know. Once it has entered, its progress is limited only by the length of the colon.

The *Balantidium coli* is a parasite which, though not so wide-spread as the ameba, in individual cases is equally serious in its effects. It does not live in the intestine in a state of harmless commensalism, but causes a dysentery which in its late stages is not amenable to medication and usually results in death.

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SUBACUTE AND CHRONIC NEPHRITIS AS FOUND IN 1,000 UNSELECTED NECROPSIES *

W. OPHULS, M.D.
SAN FRANCISCO

Ever since Bright, by his admirable papers in 1827[1] and 1836[2] established the interrelation between renal disease, albuminuria, certain types of dropsy and cardiac hypertrophy, the question of a proper classification of the cases which belong to what is commonly known as Bright's disease has been discussed with much interest, and at times with considerable animation, among clinicians and pathologists. Bright himself early in the course of his very precise clinical and anatomical investigations, during which he had also noticed in such cases a tendency to inflammations of the serous membranes and to cerebral apoplexy, was struck with the great differences in the gross appearance of the kidneys, and he seems to have favored the view that a subdivision into different groups seemed desirable but he never, according to his published writings, came to any very definite conclusion in regard to this point, although we have Wilks'[3] testimony to the effect that he favored a subdivision into two main groups on an anatomical basis, the one characterized by the development of what is even now described as a "large white kidney" and the other in which, on the contrary, small contracted kidneys were observed at autopsy. It would be entirely impossible to trace in a necessarily limited paper the historical development of the subject to the present day, however tempting it might be to do so. It may be said, however, in a general way that if all later investigators had followed Bright's shining example by studying and publishing the full facts in regard to their own cases first, before attempting to arrive at any very definite theoretical conclusions, much

*From the Pathological Laboratory of Cooper Medical College and of Leland Stanford Jr. University.

1. Bright: Report of Medical Cases, etc., London, 1827.

2. Bright: Cases and Observations Illust. of Renal Disease, etc., Guy's Hosp. Rep., 1836, i, 338.

3. Wilks: Cases of Bright's Disease, Guy's Hosp. Rep., 1853, viii, Series 2, 232.

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error and confusion might have been avoided. It is naturally somewhat cumbersome to load down one's publications with a detailed recital of the facts observed; still at a later period frequently a few facts well recorded have more value than no end of theoretical considerations, quite apart from the fact that they necessarily put some bridle on the scientific imagination of the investigator.

We may shortly recall that Toynbee[4] in England, in 1846, and later, in 1851, Reinhardt[5] and Frerichs[6] in Germany attempted to prove that the differences observed by Bright and others merely represented different phases in the same process, a view which in its generality, except as applying to certain cases, has, so far as I can see, been abandoned by all later investigators. Wilks,[3] Grainger Stewart,[7] Johnson,[8] and Dickinson[9] in Great Britain, Charcot[10] in France and Bartels[11] in Germany elaborated Bright's original conception of the essential differences between different types of chronic nephritis[12] as the process then began to be called. In 1879 Weigert[13] attempted to insist again on the essential unity at least in the histogenesis of the lesions in the kidneys in all cases of Bright's disease, not by reviving the old teaching of the different phases, through which all cases of Bright's disease would pass, but by proclaiming that the one unit which binds all these cases together was the fundamental

4. Toynbee: The Intimate Structure of the human Kidney, etc., Medico-Chir. Tr., 1846, xxix, 303.

5. Reinhardt: Die Bright'sche Nierenkrankheit, Charité Ann., 1850, i, 194.

6. Frerichs: Die Bright'sche Nierenkrankheit, Braunschweig, 1851.

7. Stewart, Grainger: On Bright's Diseases of the Kidney, Ed. 2, Edinburgh, 1871.

8. Johnson: The Minute Anatomy and Pathology of Bright's Disease of the Kidney, Medico-Chir. Tr., 1846, xxix, 1; The Inflammatory Diseases of the Kidney, Medico-Chir. Tr., 1847, xxx, 165; Certain Points in the Anatomy and Pathology of Bright's Disease of the Kidney, Medico-Chir. Tr., 1868, li, 57; Lectures on Bright's Disease, etc., London, 1874; Granular Degeneration of the Kidney, Brit. Med. Jour., 1875, i, 741.

9. Dickinson: The Pathology and Relations of Albuminuria, Brit. Med. Jour., 1876, i, 467.

10. Charcot: Lectures on Bright's Disease of the Kidney, Translation 1878.

11. Bartels: The Diffuse Diseases of the Kidneys, Ziemssen's Encyc., 1877, xv, 409. Klinische Studien über die verschiedenen Formen von chronischer diffuser Nierenentzündung, Samml. klin. Vortr. (Volkmann's), 1871, Int. Med., i, 159.

12. It is only with such subacute and chronic conditions that we are concerned in this paper.

13. Weigert: Die Bright'sche Nierenerkrankung, etc., Samml. klin. Vortr. (Volkmann's), 1879, Int. Med., ii, 1411.

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fact that in all of them there was in the kidneys primary epithelial destruction followed by more or less marked proliferative processes in the connective tissue, and that the differences observed were merely due to differences in intensity, chronicity and interrelation of these two fundamental and interdependent processes. His subdivision, based largely on the chronicity of the various changes, so far as they could be determined by histological investigation, does not seem to have proved altogether acceptable to other observers. At the present time, among pathologists, especially in Germany there seems to be a tendency to eliminate from the general picture of Bright's disease two conditions which are looked on as more or less purely degenerative in character, namely, amyloid degeneration of the kidneys on the one hand and the very common arteriosclerotic lesions which were so well studied by Ziegler,[14] on the other. This tendency is not without its opponents, however, because amyloid degeneration in the kidneys is very frequently associated with what is commonly known as chronic parenchymatous nephritis. Orth says:[15] "It is going too far to exclude every large white kidney with amyloid from the inflammatory processes." On the other hand, the differentiation between arteriosclerotic kidneys and what has been described as chronic interstitial nephritis is acknowledged to be a matter of some difficulty.

In 1897, Councilman[16] in our country published an excellent paper which he calls a study of acute diffuse nephritis but in which he also treats of subacute and chronic conditions, and on the basis of which he arrives at the following classification of the subacute and chronic cases.

Subacute glomerular nephritis
Chronic diffuse nephritis—
  A. Chronic glomerular nephritis
  B. Chronic arteriosclerotic nephritis
  C. Chronic degenerative and interstitial nephritis
Senile nephritis

Subacute and chronic glomerular nephritis represent the majority of large white and variegated kidneys; chronic arteriosclerotic nephritis

14. Ziegler: Ueber die Ursachen der Nierenschrumpfung, Deutsch. Arch. f. klin. Med., 1880, xxv, 586.

15. "Man geht zu weit, wenn man ohne weiteres jede grosse weisse Niere mit Amyloid von den eigentlichen entzündlichen Prozessen ausschliessen will."—Orth: Pathol. Anat., 1893, ii, 79.

16. Councilman: Anatomical and Bacteriological Study of Acute Diffuse Nephritis, Am. Jour. Med. Sc., 1897, cxiv, 23.

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accounts for the majority of contracted kidneys. In 1906, Councilman[17] reviewed his former work and came to the conclusion: "It is not probable that much light will be thrown on the numerous obscure questions relating to nephritis by anatomic investigation," and he emphasized the necessity of commencing all over again, so to speak, with a very thorough intensive study of individual cases by pathologists and clinicians conjointly. Jores'[18] important work seems to have emphasized the differences between chronic parenchymatous and chronic interstitial (arteriosclerotic) nephritis, and Löhlein's[19] recent careful clinical and anatomical investigations on glomerulonephritis seem to have brought out this important point that the transition of chronic parenchymatous nephritis into secondary contracted kidney does not seem, from clinical and anatomical evidence, to be so rare as was formerly believed.

It may be stated then that the tendency at present is to divide fairly strictly subacute and chronic parenchymatous or glomerulonephritis from what, for want of a better non-prejudicial term, we may call primary contracted kidney. The relation of the former to amyloid kidneys does not seem to be entirely clear, nor the relation of the latter to arteriosclerotic kidneys, although many believe that arteriosclerosis is a very important factor in its production. It is also pretty generally accepted at the present time that chronic parenchymatous nephritis may develop into secondary contracted kidney and, according to last reports, not so very rarely. Exact data on this latter point are not available.

It must be acknowledged, however, that many clinicians are not at all satisfied with any of the anatomical classifications so far offered. As early as 1880, Greenfield[20] insists that in chronic nephritis no strict subdivision is possible. A most interesting example of this point of view we find in Brault, who, in 1884,[21] in perhaps the most admirable exact anatomical treatise on renal diseases, in collaboration with Cornil, developed

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17. Councilman: The Pathology of the Kidney, Jour. Am. Med. Assn., 1906, xliv, 81.

18. Jores: Ueber die Arteriosklerose der kleinen Organarterien, etc., Virchows Arch. f. path. Anat., 1904, clxxviii, 367; Ueber Arterienveränderungen bei Nephritikern, Verhandl. Deutsch. path. Gesellsch., 1904, vii, 174.

19. Löhlein: Ueber die entz. Veränderungen der Glomeruli, etc., Arb. Path. Inst., Leipsic, 1907, No. 4.

20. Greenfield: Granular Contr. Kidney, Tr. Path. Soc. London, 1880, xxxi, 157.

21. Cornil and Brault: Etudes sur la pathologie du rien, Paris, 1884.

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a most elaborate anatomical classification of nephritis and who, in 1897,[22] insists that the present anatomical classifications of Bright's disease are unsatisfactory. He says: "The anatomical forms vary according to the intensity, the duration and the character of the irritation. . . . The most natural classification is that based on the etiology.[22]

Both Leyden[23] and Müller,[24] two of the foremost clinicians of Germany, voice the same opinion by pointing out that the diagnosis of anatomical conditions cannot be the chief aim of the clinician, and Müller proceeds to a most interesting attempt at an etiological classification which throws a flood of light on individual conditions but which, as a whole, is hardly entirely satisfactory. Herrick,[25] in Osler's "Modern Medicine," in 1909, puts great emphasis on the point that no sharp clinical or anatomical subdivision of cases of chronic nephritis is possible or desirable and then gives one of the usual anatomical classifications in lieu of something better.

Being interested in the study of experimental chronic nephritis, it seemed to me necessary to obtain first a thorough understanding of the conditions as they occur in man, and with this object in view I began to study my own material. Nothing new could be expected from a study of selected cases, but there was some hope that the natural interrelation of the various types with one another, and with associated conditions such as arteriosclerosis or amyloid, would be brought out more clearly by a complete study of a considerable series of consecutive cases embracing all conditions, with a special view to whatever renal, arterial or cardiac lesions might be present. It was to be expected that such an examination would at least show whether any of the known schemes of classification were sufficiently comprehensive to include all cases which were actually observed or whether, indeed, the different types merged into another imperceptibly as is maintained by some, or whether it is possible to find fairly clear lines of subdivision.

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22. Brault: Classification clinique des nephritides, la Presse méd., 1897, v, 72; Les formes anatomiques varient suivant l'intensité, la durée, la qualité de l'irritation." "La classification la plus naturelle devrait être basée sur l'étiologie."

23. Leyden: Ueber Nierenschrumpfung u. Nierensklerose, Ztschr. f. klin. Med., 1881, ii, 133.

24. Müller: Morbus Brightii, Verhandl. d. deutsch. Path. Gesellsch., 1905, ix, 64.

25. Herrick: Nephritis, Osler's Modern Medicine, 1909, vi, 103.

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One thousand consecutive cases seemed a sufficient number to exclude gross error from chance, yet a number not too large to allow a sufficiently intensive study and of proper handling of the material. A large majority of the necropsies used in the preparation of this paper were performed by myself personally, and microscopic sections from the most important organs of all cases were seen by me at the time. Whatever statistical material has been obtained in this manner can therefore be vouched for as being accurate, except where differences in interpretation are possible, which will be noted in its proper place. The last 200 cases were studied especially carefully with the particular object of this paper in mind, and many of the former cases were restudied thoroughly from preserved material, whenever it seemed at all desirable to do so.

The study of these cases was approached without any particular object in view and I hope, therefore, with a mind free from all bias so far as it is possible. I was frequently somewhat surprised at the results obtained and most particularly when, in the end, a complete subdivision of all cases into fairly distinct groups resulted, without any special effort in this direction.

The material studied was such as is found commonly in any large public hospital. The following data from the last 200 cases will perhaps give a more accurate idea. There were nineteen children and young adults to 20 years of age, 148 adult males and thirty-two adult females. Among both males and females, the larger number were between 40 and 60 years of age. The chief diseases encountered in these last 200 cases were as follows: Manifest tuberculosis 26.5 per cent., severe arteriosclerosis 14 per cent., malignant tumors 9.5 per cent., pneumonia 8 per cent., endocarditis 7.5 per cent., evident syphilis 3.5 per cent., cirrhosis 3 per cent., chronic sepsis 2.5 per cent., and so forth. The percentages are not unusual, except the very high percentage of severe arteriosclerosis which became evident on a close study of the individual cases only.

It is a well-known fact that entirely normal kidneys are found very rarely, especially in the later years of life. It became necessary, therefore, to establish how far it was possible to eliminate such minor changes from consideration. It might very well have been that just such more or less initial, still undeveloped lesions could have thrown much light on the histogenesis of the more advanced cases; in fact, the clew to the whole situation might have been just there. A very careful gross and microscopic study was therefore made of the last 200 kidneys, which con-

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firmed the general impression that these lesions are practically all of arteriosclerotic origin and that they do not help in elucidating any phase of our subject, except in so far as its relation to arteriosclerosis is concerned. A more detailed exposition of this part of the subject follows later.

It is interesting to note at this point that, on the whole, general arteriosclerotic lesions develop coincidently with arteriosclerotic lesions in the kidneys, but that there is no strict interdependence between the two processes, a fact, however, well established in medical literature.

The next question which naturally presented itself was whether it is possible to distinguish histologically or otherwise between these common, evidently arteriosclerotic, lesions and the severer lesions which are commonly described as "chronic interstitial nephritis," and which are said to produce the "genuine or primary contracted kidney," whether, as has been said so often, the kidneys of arteriosclerotics were different from severe nephritis with arteriosclerosis. In spite of some personal inclination toward the latter view, I have been unable to find any evidence to substantiate it. Histologically, the lesions are absolutely identical. The process evidently commences in the arterioles, the lesions in which have been especially well described by Jores[18] and his pupils. The glomeruli next become involved. The lesions in them are also well known and have been made the subject of special study by Thoma,[26] Tschistowitsch,[27] Josué and Alexandrescu,[28] Herxheimer,[29] and others. Initial stages of the process, contrary to the belief of some, are fairly frequently seen when one looks over many such specimens. They consist in the shrinkage of the glomerulus and a dense fibrous thickening of the capsule as shown in Figure 1. This thickening in the beginning is fairly cellular. The glomerulus at this stage still contains some blood and the nuclei stain well. Eventually the glomerulus collapses entirely, looses all nuclear staining and is surrounded by a thick mass of dense hyaline fibrous tissue.

26. Thoma: Zur Kenntnis der Circulationsstörung in den Nieren bei chronisch interstitieller Nephritis, Virchows Arch., 1877, lxxi, 42, 227.

27. Tschistowitsch: Die Verödung und hyaline Entartung der Malpighischen Körperchen der Niere, Virchows Arch. f. path. Anat., 1903, clxxi, 243.

28. Josué and Alexandrescu: Contribution a l'étude de l'artériosclérose du rein, Arch. de méd. exp. et d'anat. path., 1907, Series 1, xix, 1.

29. Herxheimer: Ueber die sogenannte hyaline Degeneration der Glomeruli der Niere, Beitr. z. path. Anat. u. z. allg. Path., 1909, xlv, 253.

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Even then the remnant of the glomerulus and the capsular hyalin around it stain entirely differently with the Van Gieson method. The change has usually been interpreted in this way: that as a result of the disease of the arterioles the blood-supply would be cut off from the glomerulus, which then was followed by its collapse, which in its turn would provoke the fibrous thickening of the capsule. I have the impression rather that this is only partly true and that the capsular thickening to some extent must be attributed to the extension of the proliferative process in the arterioles to the capsule.

The collapse of the tubules and the proliferation of the interstitial tissue which accompany this change in the glomeruli is also too well known to need further mention. I may say, however, that here again I cannot quite accept the idea of those who believe that the process is purely degenerative in character. In many instances, as Ziegler[14] himself, who is otherwise responsible for the opposite view, has observed, evidences of a certain degree of inflammation are quite well marked. The cellular infiltration which occurs in such cases is especially well shown in Figures 2 and 4, of which one represents an ordinary arteriosclerotic scar, the other an advanced degree of renal destruction by a similar process, and even in those cases in which it is missing, this may be due to the fact that the process has come to a standstill, which it undoubtedly does eventually in the majority of cases. Another fact which to my mind makes it impossible to accept altogether the view that the glomerular lesions are entirely primary and the collapse of the tubules and the proliferation of the connective tissue secondary, is this: that in some instances the number of affected glomeruli is much too small to account for the extensive lesions in tubules and connective tissue.

Casts are very commonly observed in the tubules in the affected areas probably on account of the stagnation of secretion. I cannot find any evidence, however, that they have any important relation to the lesions as a whole, as has been suggested by Aufrecht, in 1894,[30] and later by Ponfick.[31]

In regard to the formation of cysts (glomerular and epithelial) in such lesions, one factor has hardly received sufficient attention in their

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30. Aufrecht: Zum Nachweiss zweier Nephritisarten, Deutsch. Arch. f. klin. Med., 1894, liii, 531.

31. Ponfick: Ueber Morbus Brightii, Verhandl. Deutsch. Path. Gesellsch., 1905, ix, 49.

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production, namely, the shrinkage of the adjoining tissues. I am inclined to believe that this is quite important because of the frequent association with it of a sinous dilatation of the capillaries in the same areas which hardly admits of any other interpretation. Beer[32] has called particular attention to the frequency of cystic dilatation of the glomeruli in such cases as shown in my Figure 4, and from my experience I am certain that these cysts cannot all be explained as of congenital origin, as suggested by Aschoff.

TABLE 1.—SHOWING DISTRIBUTION OF ARTERIOSCLEROTIC LESIONS ACCORDING TO AGE AND SEX

Kidneys	1-20 Yrs.	20-40 Yrs. M.	20-40 Yrs. F.	40-60 Yrs. M.	40-60 Yrs. F.	Over 60 Yrs. M.	Over 60 Yrs. F.
Free from scars	18	7	4	6	2	1	0
Small scars	1	20	7	47	9	24	1
Large scars	0	2	1	10	4	15	1
Arteriosclerotic nephritis	0	2	0	4	1	6	0
Other renal lesions	0	4	1	1	1	0	0
Totals	19	35	13	68	17	46	2

TABLE 2.—SHOWING RELATION OF ARTERIOSCLEROTIC RENAL LESIONS TO GENERAL ARTERIOSCLEROSIS AND TO CARDIAC HYPERTROPHY IN 200 CASES

Kidneys	Blood-Vessels Elsewhere: Normal	Slight	Moderate	Marked
			General Arteriosclerosis	
Without scars	31	6	1	0
With small scars	23	52	19 1 with cardiac hypertrophy.	14 6 with cardiac hypertrophy.
With large scars	5	13	8	7 3 with cardiac hypertrophy.
With arteriosclerotic nephritis.	0	2 1 with cardiac hypertrophy.	4 4 with cardiac hypertrophy.	8 8 with cardiac hypertrophy.

Figures 1, 2, 3 and 4 I hope will illustrate sufficiently what type of process I believe to belong to this class and I may say again that, besides the mechanical moment of interference with the circulation which undoubtedly is important, the evidences of an accompanying low grade of inflammation should not be overlooked.

The distribution of the process varies very much in different cases, sometimes one finds many small foci scattered fairly regularly through the renal tissue, at other times one finds a very irregular distribution with the formation of the well-known irregular large purple scars. The rest

32. Beer: Occurrence of Cystic Changes in the Malpighian Bodies, etc., Am. Jour. Med. Sc., 1904.

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of the renal tissue may be entirely normal, but in the most advanced cases severe parenchymatous lesions are very frequently associated with it; the character of the lesions is, however, somewhat different from those which one observes in subacute and chronic parenchymatous nephritis. In many cases they are probably more or less terminal.

Early in the progress of my studies it became evident that this type of renal lesion could not be properly understood unless it was considered in conjunction with all other cases of well-developed arteriosclerosis, which were accordingly tabulated with the following gross result.

Arteriosclerosis with valvular disease, 15 cases.
Marked arteriosclerosis without cardiac hypertrophy or severe renal lesions, 58 cases.
Marked arteriosclerosis with cardiac hypertrophy
with slight renal lesions, 46 cases.
with severe renal lesions, 19 cases.
Arteriosclerotic nephritis
with cardiac hypertrophy, 25 cases.
without cardiac hypertrophy, 1 case.

The dividing line between marked arteriosclerosis with severe renal lesions and what I have termed "arteriosclerotic nephritis" is purely arbitrary; in fact many cases which on more careful examination proved to be cases of general arteriosclerosis with comparatively insignificant renal lesions were diagnosticated at the autopsy table as "chronic interstitial nephritis" with cardiac hypertrophy, etc., under the mistaken assumption that the renal lesion was the most important phenomenon. I believe that this mistake is made quite commonly and that in many of these cases, clinically and anatomically too much emphasis is placed on the condition of the kidneys.

The abstract of cases of marked arteriosclerosis without hypertrophy and Tables 3, 4 and 5 give the most important details in regard to these cases. Figure 2 shows a section of one of the kidneys with moderate arteriosclerotic lesions, and Figures 3 and 4 specimens of "arteriosclerotic nephritis."

I shall discuss the results obtained under the following headings:

1. Relation of arteriosclerosis to renal disease.

2. Occurrence of hypertension and cardiac hypertrophy in arteriosclerosis and in "arteriosclerotic nephritis."

3. Relation of these conditions to lead-poisoning and gout.

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I. RELATION OF ARTERIOSCLEROSIS TO RENAL DISEASE

Ever since the appearance of Gull and Sutton's[33] famous paper, in 1872, the relation of arterial disease to nephritis has been a very much-discussed topic. Some of Gull and Sutton's histologic findings may be open to doubt; still I believe they deserve great credit for having first suggested that there is a disease in which the arterioles throughout the body are altered, which constitutes "a general morbid change, of which contraction and atrophy of the kidneys is part and parcel." Their contentions have been disputed by many eminent authorities and just as vigorously embraced by others. One could fill pages with literary quotations for and against. Cornil and Brault,[21] for instance, in their excellent work are very much opposed to this view; Orth,[15] in his classic treatise on pathology, believes that in chronic interstitial nephritis the vascular changes are not essential and primary because their severity does not always correspond with the extent of the lesions, whereas Holsti,[34] Aufrecht,[30] and others are quite positive that in primary contracted kidneys the vascular lesions are general, that they precede the renal lesions and that many of the symptoms depend rather on them than on the associated disease of the kidneys. Ziegler,[14] in his well-known article, says positively:

> Arteriosclerosis is one of the most frequent causes of contracted kidney. Quite a proportion of small red kidneys are contracted as a consequence of arteriosclerosis. . . . The contraction of the kidney is only one manifestation of a disease of the vascular system extending over a large part of the body.
>
> (Die Arteriosklerose ist eine der häufigsten Ursachen der Nierenschrumpfung. Ein nicht geringer Theil der kleinen rothen Nieren ist in Folge von Arteriosklerose geschrumpft. . . . Die Nierenschrumpfung ist nur Theilerscheinung eines über einen grossen Theil des Körpers verbreiteten Erkrankung des Gefässsystems.)

Still he insists that sometimes arteriosclerosis in kidneys is local and secondary. Jores,[18] who in the last years has made a very careful study of arteriosclerosis and associated conditions, comes to this conclusion:

> The importance of the changes in the vessels for the destruction of the glomeruli, and thus for the development of contracted kidney, should be recog-

33. Gull and Sutton: The Pathology of the Morbid State Commonly Called Bright's Disease with Contracted Kidney (Arterio-Capillary Fibrosis), Medico-Chir. Tr., 1872, lv, 273.

34. Holsti: Ueber die Veränderungen der feineren Arterien bei granulöser Nierenatrophie, Deutsch. Arch. f. klin. Med., 1886, xxxviii, 122.

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nized in all forms of nephritis in which there is arteriosclerosis of the smallest vessels.[35]

I believe that a careful scrutiny of my cases cannot leave room for doubt in regard to the fact that the ordinary red granular contracted kidney is the result of general arteriosclerosis and that in many of these cases the general arteriosclerosis is much more important, in regard to the general condition of the patient, than the renal lesion which he may have at the same time. Bradford,[36] from a similar point of view, eliminates the red granular kidneys from Bright's disease altogether, which may seem a somewhat exaggerated position to hold but which certainly has something to commend it as it emphasizes that it is wrong to look at these conditions from the point of view of the kidney only, which is the common fault at present.

The renal lesions, on the other hand, to my mind are not purely degenerative in character. In the renal tissue, the inflammatory element in this general disease is much more evident than it is in the small arteries in which, as was first suggested by Friedemann,[37] and later very conclusively proved by Jores, the lesion consists largely in an apparently hyperplastic proliferation of the elastic tissue in the intima, whereas the inflammatory nature of the process is again much more marked in the large arteries, more especially in the aorta. Roderer[38] of Philadelphia has quite recently very clearly expressed the same opinion from a clinical point of view. He says:

"Chronic interstitial nephritis is an inflammatory disease of the arteries, possibly principally of the terminal arteries. If this be correct then chronic interstitial nephritis is not the correct term to use to describe the disease. Chronic arterial fibrosis would be a better term." "When the inflammation of the blood-vessels in the kidneys extends to the parenchyma of the kidneys, then an examination of the urine will show casts and albumen." "Because the examination of the urine shows disease, it seems to me that is the reason why chronic interstitial nephritis has been called a disease of the kidneys."

35. Die Bedeutung der Gefäss-Alteration für das Zugrundegehen der Glomeruli und damit für die Entstehung einer Schrumpfniere . . . ist für alle Formen von Nierenentzündung anzuerkennen, welche mit Arteriosklerose der kleinsten Gefässe einhergehen.

36. Bradford: Bright's Disease and its Varieties, Lancet, 1904, ii, 125.

37. Friedemann: Ueber die Veränderungen der kleinen Arterien bei Nierenerkrankungen, Virchows Arch. f. path. Anat., 1905, clxxx, 543.

38. Roderer: Symptomatology and Diagnosis of Nephritis or Bright's Disease, Jour. Am. Med. Assn., 1911, lvi, 1222.

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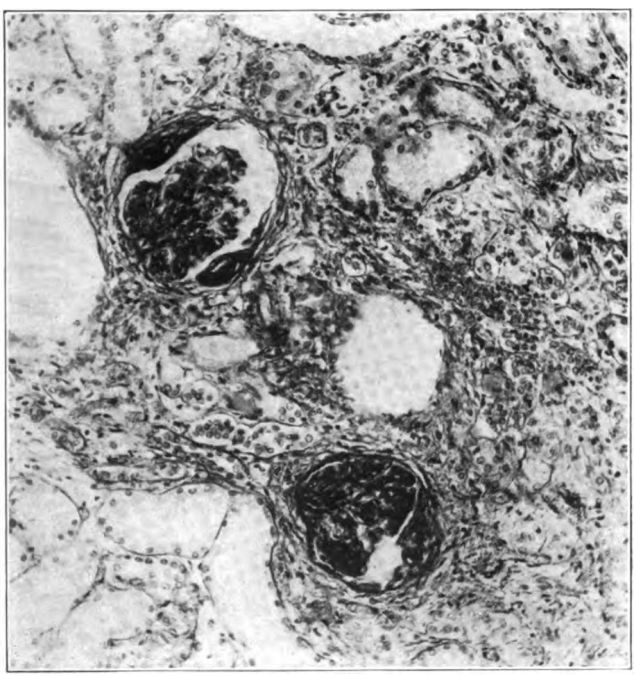

Fig. 1.—90x XII-75. Initial stage of glomerular lesions in arteriosclerosis.

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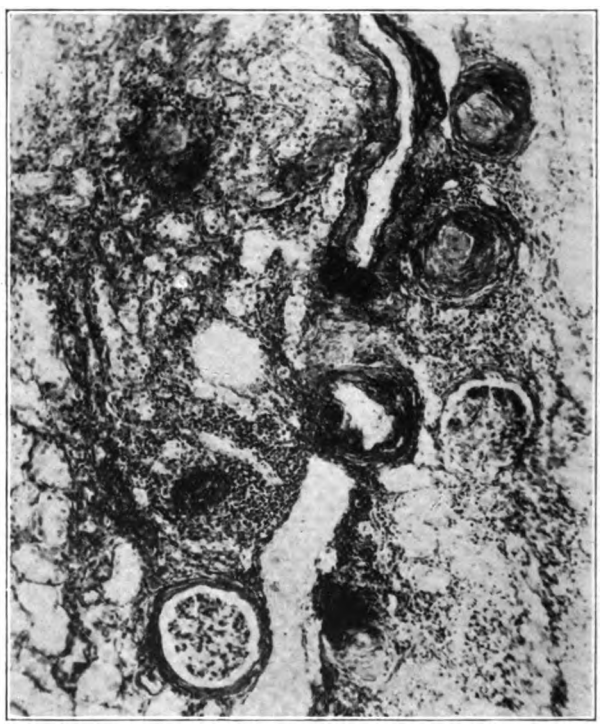

Fig. 2.—90x VIII-45. Large arteriosclerotic scar with considerable cellular infiltration.

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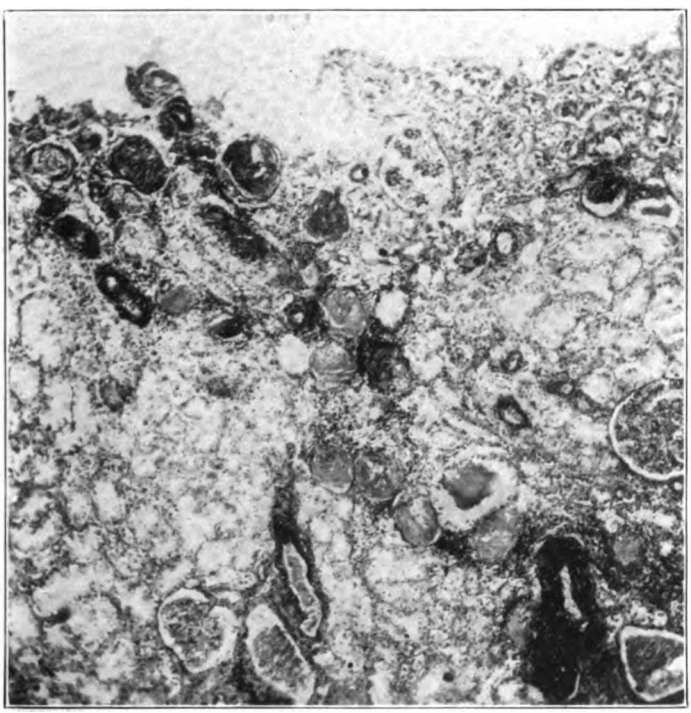

Fig. 3.—50x III-10. Focus of arteriosclerotic nephritis. Many hyaline glomeruli. Few cysts.

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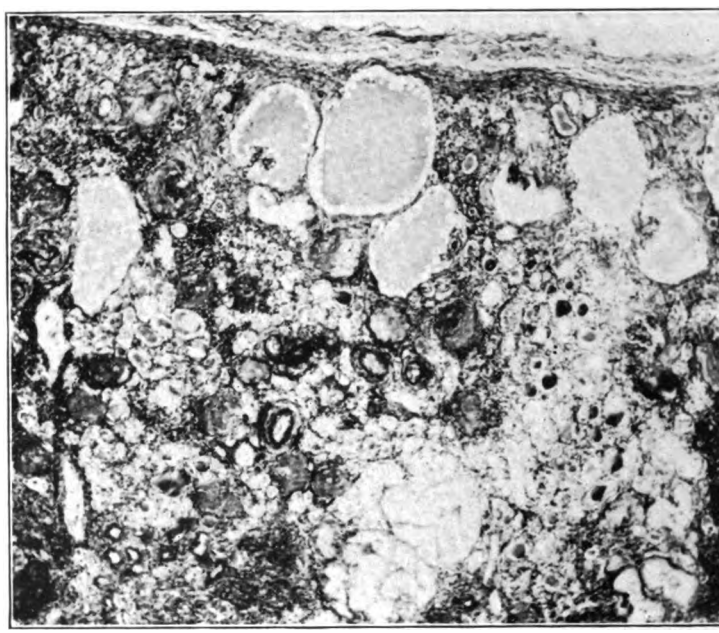

Fig. 4.—50x VII-99. Marked arteriosclerotic nephritis. Considerable cellular infiltration. Many cysts. Few hypertrophic remnants of normal tissue.

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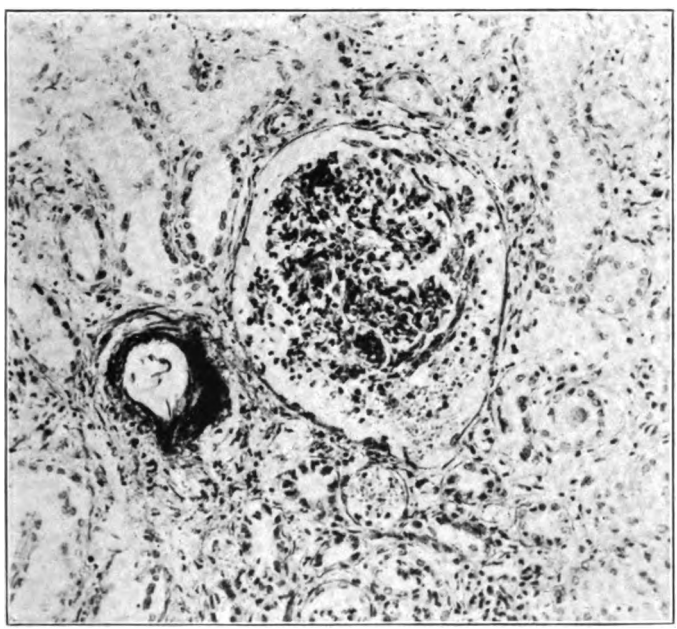

Fig. 5.—150x VIII-70. Glomerulonephritis. Acute stage. Leukocytes and blood in glomerulus. Beginning proliferation.

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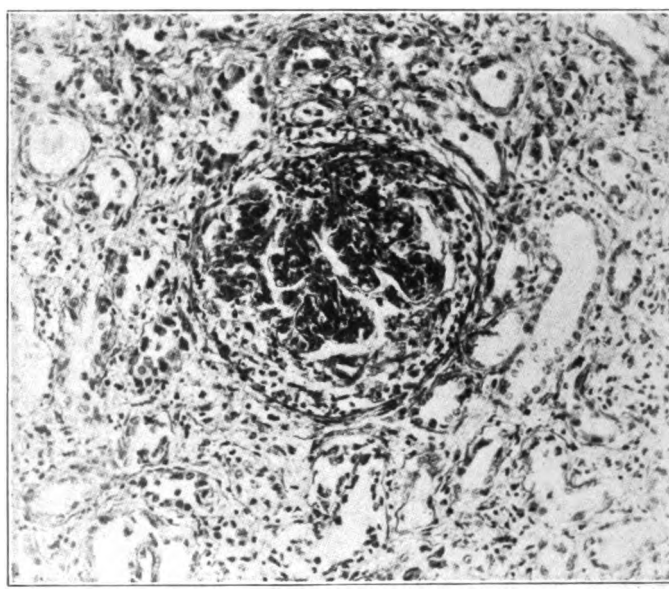

Fig. 6.—150x VIII-70. Glomerulonephritis. Later stage.

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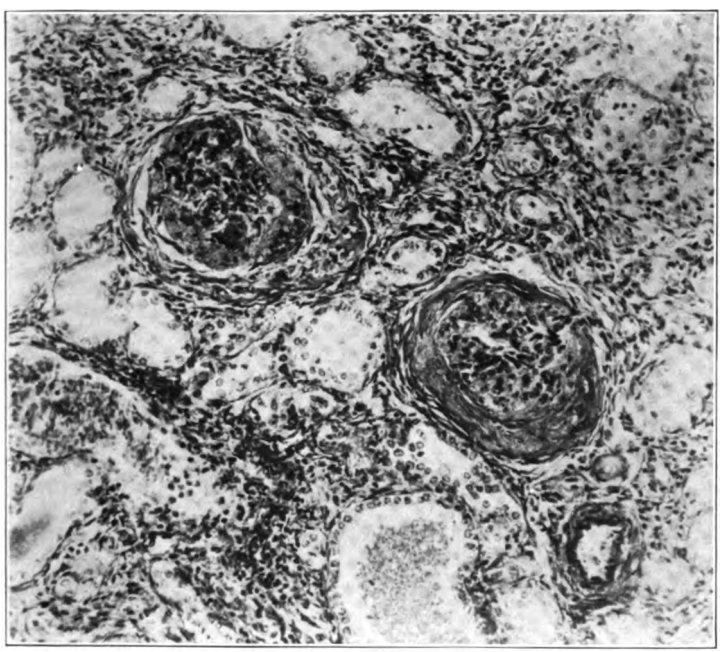

Fig. 7.—150x V-147. Glomerulonephritis. Still later stage. Beginning interstitial lesions.

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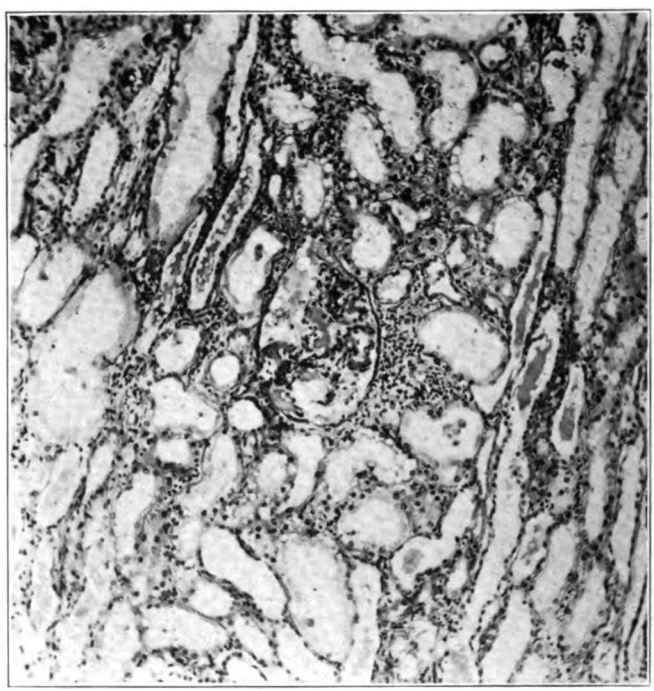

Fig. 8.—90x II-4. Parenchymatous nephritis and amyloid. Large white kidney. Beginning glomerulonephritis, beginning interstitial lesions.

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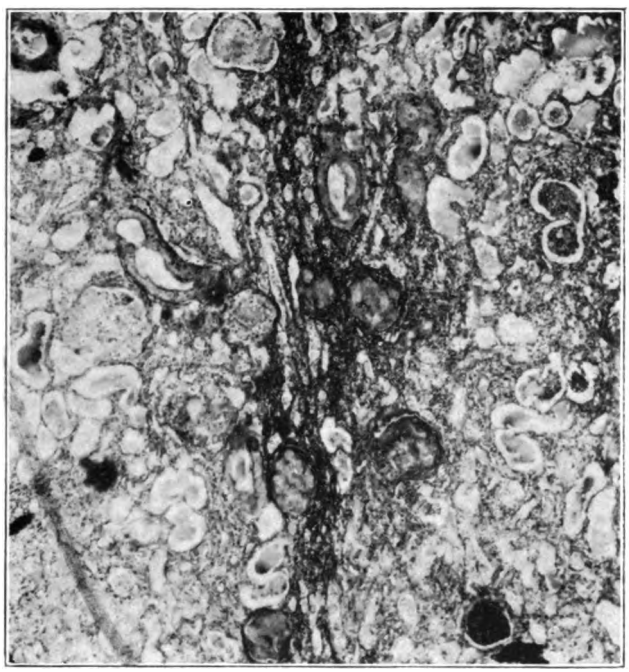

Fig. 9.—50x VIII-94. Parenchymatous nephritis and amyloid. Large white kidney. Advanced glomerulonephritis and advanced interstitial lesions.

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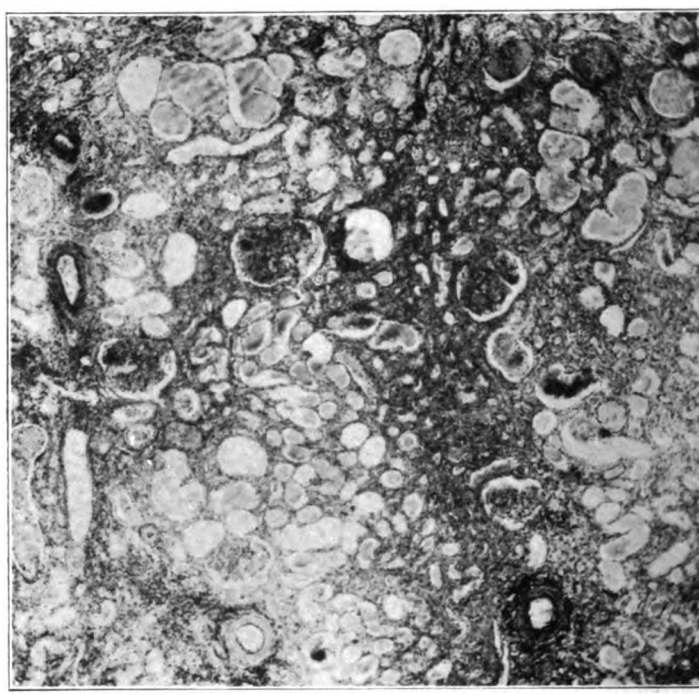

Fig. 10.—50x VIII-47. Parenchymatous nephritis and amyloid. Secondary contracted kidney. Little local amyloid. Moderate glomerulonephritis. Very marked parenchymatous and interstitial lesions. Obscure sepsis.

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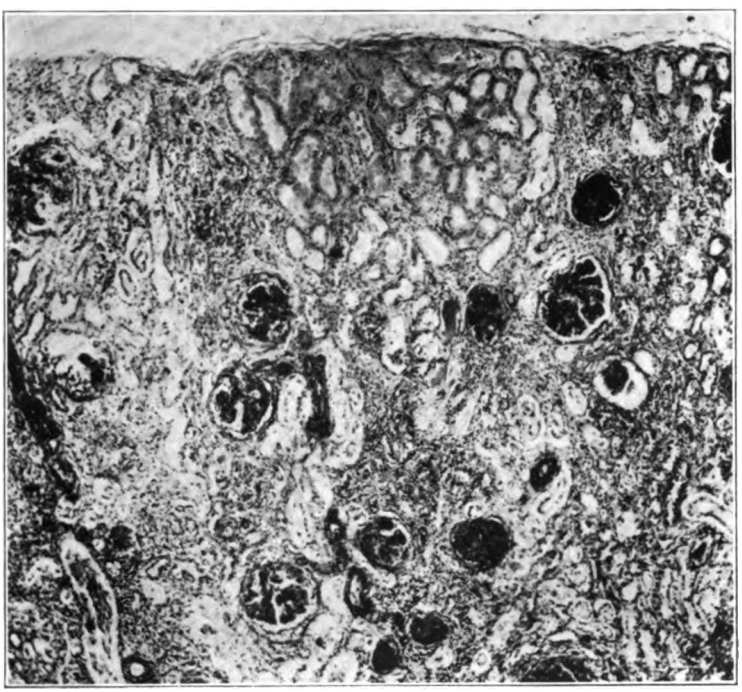

Fig. 11.—50x VIII-22. Parenchymatous nephritis and amyloid. Secondary contracted kidney. Little local amyloid. Marked glomerulonephritis. Marked diffuse interstitial lesions. Obscure sepsis.

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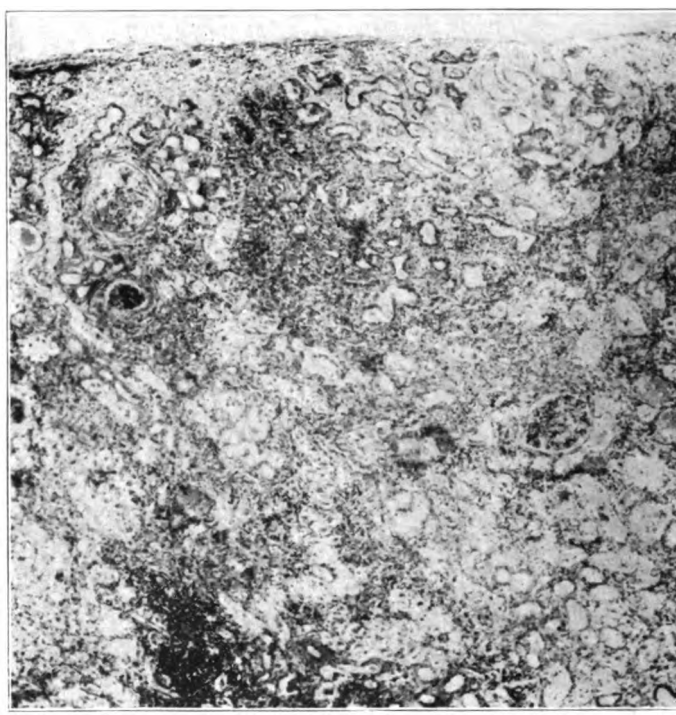

Fig. 12.—50x VII-39. Parenchymatous nephritis and amyloid. Secondary contracted kidney. Little local amyloid. Marked glomerulonephritis. Extreme diffuse interstitial lesions. Obscure sepsis.

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II. OCCURRENCE OF HYPERTENSION AND CARDIAC HYPERTROPHY IN ARTERIOSCLEROSIS AND ARTERIOSCLEROTIC NEPHRITIS

What are the facts in regard to the relation of vascular and renal disease to hypertension and cardiac hypertrophy?

In a little over one-third of our cases of marked general arteriosclerosis there is no cardiac hypertrophy. These cases are very briefly abstracted below. As shown there, this lack of evidence of hypertension may be due to general malnutrition in thirty-one cases, although, as Jores[39] has correctly pointed out, malnutrition is no bar to cardiac hypertrophy when caused by other conditions; there are also in addition six cases, or fifteen cases all told, in which the lack of cardiac hypertrophy might be referred to the more or less localized character of the arteriosclerotic lesions, it being a matter of common experience that rapidly developing aortic lesions, with aneurysms particularly, are not very apt to produce cardiac hypertrophy. There remain twenty-one cases, or well over 10 per cent. of all cases, in which no reason for the absence of cardiac hypertrophy seemed evident so far as I could see.

Abstract of Cases of Marked Arteriosclerosis without Cardiac Hypertrophy

A—Probably owing to general malnutrition due to:

1. Malignant Tumor

1. 1-18, marked atheroma of entire aorta, carcinoma of stomach.
2. 1-26, marked atheroma of aorta with fusiform aneurysm of arch, carcinoma of stomach.
3. 1-50, marked atheroma of aorta, marked peripheral arteriosclerosis with scars in heart and in kidneys, carcinoma of sigmoid flexure.
4. III-24, marked atheroma of aorta and peripheral arteriosclerosis, arteriosclerotic scars in kidneys, carcinoma of esophagus.
5. III-120, marked atheroma of aorta with dilatation, carcinoma of stomach.
6. V-40, marked atheroma of aorta, arteriosclerotic scar in left kidney, carcinoma.
7. VII-10, marked atheroma of aorta with multiple aneurysms, carcinoma of esophagus.
8. VIII-75, normal aorta, marked peripheral arteriosclerosis, carcinoma of stomach.
9. IX-52, marked atheroma of aorta and peripheral arteriosclerosis, few arteriosclerotic scars in kidneys, endothelioma of neck and cirrhosis.

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39. Jores: Ueber die Beziehungen der Schrumpfniere zur Herzhypertrophie vom pathol. anat. Standpunkt, Deutsch. Arch. f. klin. Med., 1908, xciv, 1.

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2. Senility

10. I-25, marked atheroma of aorta with aneurysm of thoracic aorta; old woman.

11. I-77, marked atheroma of aorta and peripheral arteriosclerosis, peptic ulcer, senile atrophy of all organs.

12. III-27, marked atheroma of aorta and peripheral arteriosclerosis, several small aneurysms in splenic artery and scars in myocardium; extremely emaciated old woman.

13. IV-7, marked atheroma of aorta; emaciated man of 80.

14. IV-88, localized atheroma of arch with aneurysm; emaciated man of 74.

15. V-70, marked atheroma of aorta with fusiform aneurysm of arch; emaciated man of 62.

16. VI-79, moderate atheroma of aorta, moderate arteriosclerosis of cerebral arteries, old hemorrhages in brain; fairly strong woman of 71.

17. VII-101, marked atheroma of aorta, aneurysm of arch. large arteriosclerotic scars in kidneys, beginning amyloid; emaciated man of 69.

18. VIII-60, localized atheroma of thoracic aorta with aneurysm; emaciated man of 66.

19. IX-10, marked atheroma of aorta, moderate peripheral arteriosclerosis, few small arteriosclerotic scars in kidneys; moderately well-nourished old woman.

20. XIII-20, very marked atheroma of aorta, marked peripheral arteriosclerosis, large arteriosclerotic scars in kidneys; extremely emaciated old man.

3. Chronic Pulmonary Tuberculosis

21. III-79, marked atheroma of aorta with aneurysm of arch, chronic pulmonary tuberculosis.

22. VIII-42, marked atheroma of thoracic aorta, large arteriosclerotic scars in kidneys, chronic pulmonary tuberculosis; emaciated man of 58.

23. XIII-8, slight atheroma of aorta, slight peripheral arteriosclerosis, large arteriosclerotic scars in kidneys, pulmonary tuberculosis.

24. XIII-84, very marked atheroma of aorta, large arteriosclerotic scars in kidneys, chronic pulmonary tuberculosis, emaciation.

4. Chronic Syphilis

25. XII-82, marked atheroma of thoracic aorta, marked arteriosclerosis of cerebral and renal arteries, few small arteriosclerotic scars in kidneys, syphilitic meningomyelitis; emaciated old man.

5. Chronic Gastric Ulcer

26. VIII-10, no atheroma of aorta, marked peripheral arteriosclerosis, large arteriosclerotic scars in kidneys, peptic ulcer; emaciated man of middle age.

6. Chronic Suppuration

27. I-93, marked atheroma of thoracic aorta with beginning formation of aneurysm, less of abdominal aorta, hematomyelia, emaciated from chronic suppurative cystitis and pyelitis.

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7. *Addison's Disease*

28. I-43, marked atheroma of aorta, Addison's disease.

8. *Unknown Cause, Probably Syphilis*

29. III-54, local atheroma of descending aorta and aneurysm; emaciated negro of 41.

30. VII-2, localized atheroma of thoracic aorta with moderate dilatation; emaciated man of 52.

31. VII-106, localized atheroma of arch with aneurysm; emaciated man of 40.

B.—POSSIBLY ON ACCOUNT OF LOCALIZED CHARACTER OF LESIONS

32. VI-10, localized atheroma of arch with aneurysm, aorta otherwise normal; strong, well-nourished, syphilitic of 29.

33. VI-125, marked atheroma of aorta, aneurysm of arch; strong old man.

34. VI-126, marked atheroma of aorta, with dilatation of aorta; strong man of 58.

35. VII-35, marked atheroma of entire aorta; stout man of 45.

36. VII-72, marked localized atheroma of arch, sarcoma of brain; muscular well-nourished man of 42.

37. VIII-69, localized atheroma of thoracic aorta with aneurysm; strong man, middle age.

The limited extent of the lesions may also play a rôle in Cases I-18, 25, 26, 43, 93, III-54, 79, 120, IV-7, 88, V-70, VII-2, 10, 106, VIII-60 of Series A, in which the disease is more or less confined to the aorta, and in XIII-8 in which case the lesions are severe in kidneys only.

C.—UNEXPLAINED

38. III-1, marked atheroma of aorta with aneurysm of arch, few scars in left ventricle; strong, moderately well-nourished man of 50.

39. III-80, marked atheroma of aorta with dilatation, moderate arteriosclerotic lesions in kidneys, old apoplectic cyst in brain; strong man of 60.

40. V-126, marked atheroma of aorta, moderate peripheral arteriosclerosis, arteriosclerotic scars in kidneys; strong well-nourished man of 68.

41. VI-77, marked atheroma of aorta, marked peripheral arteriosclerosis, arteriosclerotic scars in kidneys; strong muscular man.

42. VII-84, marked atheroma of entire aorta with beginning dilatation of arch, small arteriosclerotic scars in kidneys; strong old man.

43. VII-92, localized atheroma of arch with aneurysm, many small arteriosclerotic scars in kidneys; strong man of 49.

44. VII-94, marked atheroma of aorta, marked general arteriosclerosis, many small arteriosclerotic scars in kidneys, diabetes; strong, stout man.

45. VIII-29, marked atheroma especially of abdominal aorta, considerable peripheral arteriosclerosis involving coronary and cerebral arteries, small arteriosclerotic scars in kidneys; fairly well-nourished man of 70.

46. VIII-30, marked atheroma of aorta, marked peripheral arteriosclerosis, arteriosclerotic scars in kidneys; strong man of 83.

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47. VIII-59, slight atheroma of aorta, marked arteriosclerosis of cerebral and of coronary arteries with softening of brain and scars in myocardium; strongly built, fairly well-nourished old man.

48. VIII-97, marked atheroma of aorta, slight arteriosclerotic lesions in kidneys; well-nourished old man.

49. IX-2, marked atheroma of aorta, aneurysm of left iliac artery, marked arteriosclerosis of peripheral arteries, obstruction of coronaries; fairly well-nourished man of 59.

50. IX-12, localized atheroma of thoracic aorta, moderate arteriosclerosis of coronary arteries, large arteriosclerotic scars in left kidney; strong man of middle age.

51. IX-38, marked atheroma of aorta with aneurysm, many small arteriosclerotic scars in kidneys; strong man of 66.

52. IX-58, moderate atheroma of aorta, and marked peripheral arteriosclerosis, large arteriosclerotic scars in kidneys, cerebral softening, necroses in myocardium, gastric ulcer; muscular, well-nourished man of 61.

53. IX-60, moderate atheroma of aorta, with dilatation, marked peripheral arteriosclerosis with dilatation, few arteriosclerotic scars in kidneys; strong old man.

54. XII-8, slight atheroma of aorta, large arteriosclerotic scars in kidneys, diabetes; strong, well-nourished man of 60.

55. XII-29, marked atheroma of aorta, area of softening in brain, many small arteriosclerotic scars in kidneys; strong man of 59.

56. XII-67, marked atheroma of aorta, marked general arteriosclerosis, arteriosclerotic scars and necroses in myocardium, few small arteriosclerotic scars in kidneys; strong man of 45.

57. XIII-27, marked atheroma of aorta, aneurysm of abdominal aorta, moderate peripheral arteriosclerosis, large arteriosclerotic scars in kidneys; strong man.

58. XIV-3, very marked atheroma of aorta, aneurysm of abdominal aorta, few arteriosclerotic scars in kidneys; fairly well-nourished man of 50.

SUMMARY

Marked arteriosclerosis without cardiac hypertrophy in fifty-eight cases, 35 per cent. of all cases of marked arteriosclerosis.

Lack of cardiac hypertrophy, possibly due to general malnutrition in thirty-one cases.

Malnutrition due to:	Cases
Tumor	9
Senility	11
Chronic tuberculosis	4
Chronic syphilis	1
Chronic gastric ulcer	1
Chronic suppuration	1
Addison's disease	1
Unknown cause, probably syphilis	3
	31

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Lack of cardiac hypertrophy possibly due to localized character of lesions in six cases, perhaps also in fifteen of those mentioned before.

Lack of cardiac hypertrophy unexplained in twenty-one cases.

If we look over the cases with cardiac hypertrophy in Tables 3, 4 and 5, we notice that, on the whole, the devolopment of the cardiac lesion is associated much more closely with the degree of arteriosclerosis present than with the extent of the renal lesions.

In the cases, for instance, represented in Table 3, the renal lesions are those which are so very commonly found at autopsy in otherwise healthy kidneys. It seems highly improbable, therefore, that they were concerned in any way in the production of the general condition. The cardiac hypertrophy in many of these cases is very well marked, just as much so as in cases with advanced renal lesions, and this has eventually led to the usual disturbances in the general circulation. There is well-marked evidence that the process in the heart begins with a concentric hypertrophy of the left ventricle, followed by insufficiency and dilatation, later involves the pulmonary circulation and the right ventricle and ends in general passive congestion and an entire breakdown of the circulatory mechanism. In 1884, Lemcke[40] gave an excellent clinical and anatomical description of a very interesting case which evidently belongs to this first group.

In Group 2 also (Table 4) the renal lesions are comparatively insignificant. Here again we encounter the same condition of affairs.

In Group 3 (Table 5) that of "arteriosclerotic nephritis," of which I wish to emphasize again that it is not separated by any sharp boundary from Group 2, there is one case without any cardiac hypertrophy, for the lack of which there is no explanation so far as I can see (see Case 1-III-75). The others show cardiac hypertrophy but in fully six of the twenty-six it is only slight, which in Cases 3 and 5 might be explained by the sudden early death of the individuals; still the fact remains that Patient 5 at least, in addition to the marked disease of the kidneys, had a well-developed general arteriosclerosis. There are four more similar cases, in which the hypertrophy of the left ventricle is only moderate, which leaves a well-marked cardiac hypertrophy in a little over half the cases only.

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40. Lemcke: Beitrag zur Lehre von den ursächlichen Beziehungen zwischen chronischer interstitieller Nephritis und Endarteritis obliterans der kleinen Arterien des ganzen Körpers, Deutsch. Arch. f. klin. Med., 1884, xxxv, 148.

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Table 2, however, seems to suggest that the condition of the kidneys after all may be of some importance in the production of the cardiac hypertrophy because, as is shown there, among the last 200 cases examined there were fourteen cases of marked general arteriosclerosis with small scars in the kidneys. Only six of these showed cardiac hypertrophy. There were also seven cases of marked general arteriosclerosis with large scars in the kidneys — cardiac hypertrophy in three, whereas among eight cases of marked general arteriosclerosis with "arteriosclerotic nephritis," cardiac hypertrophy was present in all.

If we now inquire whether we ever find cardiac hypertrophy without marked arteriosclerosis and without renal lesions, not attributable to the usual other causes for such a condition, we find among the 1,000 necropsies three cases which show this condition. These cases are summarized below. There is some arteriosclerosis in all of them but certainly not enough to account for the marked cardiac hypertrophy. In the first case (I-107) the chronic bronchitis and emphysema which is present might explain changes on the right side of the heart but not, at least according to my experience, the general hypertrophy and dilatation of the entire heart. In the second and third case there is not even that much of an explanation to be found, unless one wanted to look on Case 2 as a beer-drinker's heart, which, to my idea, has a somewhat uncertain standing in pathology. These cases are very similar to a case described by Jores,[39] with slight peripheral arteriosclerosis, slight renal lesions and yet marked cardiac hypertrophy without apparently any adequate cause for the latter, except arterial hypertension of unknown origin. It may be well to emphasize that these cases do not represent Huchard's "presclerosis," because the general symptom-complex of an old chronic condition with cardiac edema, thrombosis, embolism, etc., is fully developed.

Summary of Cases of Hypertrophy of the Left Side of the Heart Without Valvular Disease and Without Marked Arteriosclerosis

Case 1.—I. 107—C. W., stout woman of middle age; heart very much enlarged, between two and three times size of fist, considerable hypertrophy and dilatation of both sides of heart, very slight atheroma of aorta, marked arteriosclerosis in spleen, slight arteriosclerosis elsewhere, with few small arteriosclerotic scars in kidneys. Barrel-shaped thorax, purulent bronchitis, emphysema of lungs. General passive congestion, anasarca, ascites, hydrothorax; recent fibrinous pericarditis.

Case 2.—V. 90.—P. C., waiter, 68 years; marked hypertrophy and dilatation of both sides of the heart, very slight atheroma and slight dilatation of aorta, marked arteriosclerosis in spleen, no arteriosclerotic lesions in kidneys or else-

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where; slight emphysema, somewhat barrel-shaped thorax, general cyanosis and edema, ascites, hydrothorax. Brown induration of lungs. Thrombi in periprostatic veins, emboli in pulmonary artery; thrombosis in left ventricle, infarctions in kidneys.

CASE 3.—V. 54—W. T. F., strong old man; heart very large, nearly three times size of fist, hypertrophy more marked on left side; moderate arteriosclerosis of coronary arteries without obstruction, no arteriosclerotic lesions in kidneys or elsewhere; cerebral arteries normal; several old infarctions in kidneys, several areas of probably embolic softening in brain; cholelithiasis and chronic pancreatitis; old fibrinous pericarditis; death from lobar pneumonia.

Jores also showed that hypertension in the arteries, such as sometimes exists in valvular disease, does not apparently lead to arteriosclerosis but to hypertrophy of the media of the small arteries. Still, he does not seem to be ready to abandon his original conception, one which at present seems to have so many adherents (see Elliott[41] and Frank[42]), namely that the hypertension is the primary trouble which leads to both cardiac hypertrophy and general arteriosclerosis. The latter would then appear largely as an excessive compensatory process followed by degenerative lesions.

It also seems quite evident from my cases that general arteriosclerosis cannot be the direct cause of the hypertension which produces the cardiac hypertrophy.

The theory of Hasenfeld,[43] that hypertension results only when the splanchnic area is affected by arteriosclerosis, is borne out by my own observations.

Actual observation then shows (1) that there may be marked general arteriosclerosis affecting the peripheral vessels without continued hypertension; (2) that the same is more rarely true when the arteriosclerosis is associated with extensive destruction of the kidneys; (3) that, at times, we have long-continued hypertension and cardiac hypertrophy, followed by cardiac insufficiency, of unknown origin, with little arteriosclerosis and slight renal lesions.

This demonstrates, to my mind, that (4) the interrelation between general arteriosclerosis, arteriosclerotic renal disease, on the one hand, and hypertension with resulting cardiac hypertrophy, on the other hand, must be a rather loose one. Jores[39] suggests that hypertension and arterial disease coordinate, or as he expresses it also:

41. Elliott: Arterial Hypertension, Am. Jour. Med. Sc., 1910, cxxxix, 648.

42. Frank: Beziehungen zwischen Niere, Nebenniere und hohem Blutdruck in der menschlichen Pathologie, Berl. klin. Wchnschr., 1911, xlviii, 609.

43. Hasenfeld: Ueber Herzhypertrophie bei Arteriosklerose, etc., Deutsch. Arch. f. klin. Med., 1897, lix, 215.

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"Hypertrophy and arteriosclerosis appear to be forms of differently placed reactions of the vascular system to one and the same injury." [44]

I believe we must go much farther than this. The evidence demands, to my mind, that we look on these conditions as frequently associated with one another but not directly connected. Jores' assumption of a noxa which at the same time affects the heart and the arteries, producing hypertrophy in the one and arteriosclerosis in the other, does not suffice to cover the situation.

The three cases summarized above seem to me to be a very serious argument against the proposition that hypertension in itself alone can be looked on as an adequate cause for general arteriosclerosis, because in these cases there was evidently long-continued considerable hypertension and still there was very little arteriosclerosis. Nor is an argument quite satisfactory which might be suggested by Senator's[45] paper in 1897 namely that the conditions are so frequently associated because their etiology is similar. It is true, in his paper Senator speaks of the interrelation of arteriosclerosis and chronic nephritis only, pointing out that senility, gout, lead, alcohol, syphilis, diabetes, tobacco, abnormal hereditary influences, seem to injure both arteries and kidneys simultaneously. One might, however, wish to apply this idea to the more general question of the relation of hypertension to arteriosclerosis and arteriosclerotic renal disease as well, but the mere fact that the poisons suggested as active in these cases do not necessarily cause hypertension would speak against this idea.

From the evidence at hand we can only say: General arteriosclerosis is a frequent disease probably of toxic origin (this would, to my mind, explain the evidences of inflammation in the larger arteries and in the kidneys). It is often the cause of a peculiar type of renal disease. It is frequently but by no means regularly associated with hypertension and cardiac hypertrophy.

III. THE RELATION OF LEAD-POISONING AND GOUT TO GENERAL ARTERIOSCLEROSIS AND ARTERIOSCLEROTIC NEPHRITIS

I have had occasion to point out before that lead is the only definite etiological factor known in this type of renal lesion. Attempts have been

44. Hypertrophie und Arteriosklerose erscheinen als verschieden lokalisierte Reaktionen des Gefässsystems auf dieselbe Schädigung.

45. Senator: Die Pathogenese der chronischen Nephritis, Berl. klin. Wchnschr., 1897, xxxiv, 820.

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TABLE 5.—ARTERIOSCLEROTIC NEPHRI

The kidneys of the third series resemble very closely those in the second series, only the lesi The surface is granular, often full of large, deep scars. The color of the kidneys is usually a da described as diffusely pale (white contracted kidneys). The kidney tissue is very hard. The si On the cut surface the cortex is always found much reduced, to approximately 2-3 mm. in diame specimens the cortex was full of cysts of varying sizes. This was particularly noticeable in Cas "granular atrophy" or as "the red contracted kidney" by the English authors.

Number	General Condition	Aorta	Peripheral Art.	
1. III-75...	Stout old man.....	Marked atheroma	Marked arteriosclerosis.	Brow
2. VIII-91.	Emaciated woman of 41	Slight atheroma	Marked arteriosclerosis.	Sligh
3. VI-56...	Emaciated man of 60...	Normal	Slight arteriosclerosis..	Sligh
4. XIII-33.	Emaciated young man; lead anemia.	Atrophic	Mod. arteriosclerosis ...	Sligh
5. XIII-42.	Strong man of 50.....	Moderate atheroma	Marked arteriosclerosis.	Sligh
6. V-91....	Moderately strong man of 69; painter.	Normal	Little arteriosclerosis except in kidney.	Sligh
7. I-101...	Fat old man.....	Marked atheroma	Little arteriosclerosis except in kidney.	Sligh
8. XII-32..	Strong man of 65.....	Marked atheroma	Marked arteriosclerosis.	Large
9. III-10...	Emaciated man of 62...	Marked atheroma	Mod. arteriosclerosis ...	Mode
10. XIII-76.	Emaciated man of 65...	Moderate atheroma	Marked arteriosclerosis.	Mode ver
11. I-16....	Strong old man.....	Moderate atheroma	Mod. arteriosclerosis ...	Mode ver
12. I-109...	Fairly strong man of 37	Slight atheroma	Marked arteriosclerosis; gastric ulcer.	Mark ven
13. I-2.....	Strong man	Marked atheroma	Marked arteriosclerosis.	Mark ven
14. VII-108.	Strong old man; painter	Slight atheroma	Mod. arteriosclerosis ...	Mark dil
15. VIII-34.	Emaciated man of 48; painter.	Normal	Little arteriosclerosis except in kidneys.	1¼ × hy
16. XIII-86.	Strong man of 64.....	Moderate atheroma	Marked arteriosclerosis.	1¼ × som
17. VII-79..	Emaciated man of 60...	Considerable atheroma..	Marked arteriosclerosis.	1½ × of
18. VIII-55.	Emaciated man of 77...	Marked atheroma	Marked arteriosclerosis in kidneys.	1½ ×
19. V-18....	Stout man of 62.....	Slight atheroma	Marked arteriosclerosis.	1½ × tio
20. VII-99..	Anemic man of 41.....	Normal	Little arteriosclerosis except in kidneys.	1½ × mo
21. XII-43..	Emaciated woman of 42	Marked atheroma	Marked general arteriosclerosis.	1½-2 tro dil
22. IX-57...	Strong man of 65.....	Marked atheroma	Mod. arteriosclerosis except in kidneys.	2-3 × dil and
23. XIII-70.	Anemic man of 70.....	Slight atheroma	Mod. arteriosclerosis ...	2 × no ata
24. VII-59..	Strong man of 49.....	Marked atheroma	Mod. arteriosclerosis; scars in heart-muscle.	3-4 × mo
25. XIII-100	Emaciated man of 79; anemic.	Marked atheroma	Marked arteriosclerosis; scars in heart-muscle.	Very of
26. XIII-103	Anemic man of 31.....	Slight atheroma	Mod. arteriosclerosis ...	Very som

TABLE 6.—ACUTE AND S

Number and Age	Probable Cause	Heart	Blood-Vessels	Kidneys: Gr
1 III-8 23 yrs.	Chronic septic endocarditis.	Hypertrophy due to valvular disease.	Normal.	Cortex swollen, o tions.
2 II-1 Middle age.	Chronic pulmonary tuberculosis; streptococcus sepsis.	Brown atrophy.	Slight atheroma of aorta.	13½ × 5½ × 4½ brown, full of cortex opaque, ed
3 VIII-84 Middle age.	Subacute septic endocarditis.	Hypertrophy due to valvular disease.	Normal.	13 × 3 × 3½ cm. noticed.
4 VII-32 Middle age.	Pneumococcus sepsis following compound fracture of tibia.	Normal.	Normal.	16 × 7½ × 5 cm.; full of hemorrha
5 VIII-19 40 yrs.	Subacute septic endocarditis.	Hypertrophy due to valvular disease.	Normal.	12½ × rha

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ΓIS ARRANGED ACCORDING TO SIZE OF HEART

ons are of a much more extreme degree. The capsule is noted adherent in all except in one case (V-18). ırk purple, mottled, with lighter gray or yellowish spots; in a few instances the kidneys, however, are izes vary from 15x5x3½ cm. (with some hypertrophy of the fatty tissue around the renal pelvis) to 8x4x5 ter. The markings of the cut surface are described as poor "or indistinct" in all cases. In several es XIII-86 and XII-43. The cases, then, are typical examples of what is commonly described as advanced

Heart	Condition of General Circulation	Other Important Lesions
n atrophy	Good	Died after prostatectomy; gouty deposits in kidneys.
tly enlarged	Good	Chronic tuberculosis of lungs.
tly enlarged	Good	Lobarpneumonia; gouty deposits in kidneys.
t hypertrophy of left ventricle	Slight recent disturbance	Gouty deposits in kidneys.
t hypertrophy of left ventricle	Good	Acute anemia following operation.
t hypertrophy of left ventricle	Good	Gouty deposits in kidneys and joints.
t hypertrophy of left ventricle	Good	Suppurative pyelonephritis; gouty deposits in kidneys, joints, skin; term. sepsis.
; and firm	Good	Gouty deposits in kidneys.
rate hypertrophy of left ventricle.	Good	Carcinoma of esophagus.
rate concentric hypertrophy of left ıtricle.	Good	Cerebral hemorrhage; gouty deposits in kidneys.
rate concentric hypertrophy of left ıtricle.	Good	Hemorrhagic diathesis.
ed concentric hypertrophy of left .tricle.	Good	Acute pericarditis and peritonitis.
ed concentric hypertrophy of left .tricle.	Marked chronic disturbance	Gangrenous ulcer on leg.
ed concentric hypertrophy of left, ıtation of right ventricle.	Good	Lead anemia; drop wrist; gouty deposits in kidneys and joints.
normal; concentric hypertr. of left, ıertr. and dilat. of right ventricle.	Good	Lead anemia; drop wrist; gouty deposits in kidneys and joints; pericarditis.
; normal; marked hypertr. of left, ıe hypertr. and dilat. right ventricle.	Good	Multiple hemorrhagic foci in brain.
normal; marked concentric hypertr. left, slight hypertr. right ventricle.	Marked chronic disturbance	Chronic ulcer on back of left foot.
normal	Good	Unresolved pneumonia; pericarditis.
; normal; hypertrophy and dilata- ı of both sides.	Marked recent disturbance.	.....
normal; concentric hypertr. of left, ı. hypertr. and dilat. of right heart.	Marked subacute disturb...	Gouty deposits in kidneys.
X normal; marked concentric hyper- ɔhy of left, some hypertrophy and ıtation of right ventricle.	Marked recent disturbance.	.....
normal; marked hypertr., slight ıtation of left ventricle, hypertr. ı dilatation of right ventricle.	Marked subacute disturb...	Gouty deposits in kidneys; recent pleurisy.
rmal; marked hypertrophy and dil- tion of both sides.	Marked chronic disturbance	Acute dysentery; gouty deposits in kidneys.
normal; marked hypertrophy and lerate dilatation on both sides.	Marked chronic disturbance	Gouty deposits in kidneys.
large; hypertrophy and dilatation ɔoth sides.	Marked chronic disturbance	Chronic emphysema.
large; marked hypertrophy of left, ıe dilatation of right side.	Slight recent disturbance	Cerebral hemorrhage; gouty (?) deposits in kidneys.

UBACUTE GLOMERULONEPHRITIS

ɔss Appearance	Kidneys: Microscopical Lesions
ɔaque, some infarc-	Septic embolus; anemic necrotic infarct; no arteriosclerosis; leukocytosis in hyperemic glomeruli; in some, necrosis of few loops and beginning glomerulonephritis; blood in many tubules; few small foci near glomeruli show diffuse infiltration with polymorphonuclear leukocytes and beginning proliferation of connective tissue.
cm.; dark reddish small hemorrhages; ematous.	No arteriosclerosis; glomeruli anemic; swollen; very cellular; capsular spaces wide; no desquamation of epithelium; much hemorrhage in tubules; pigmented casts.
; no gross lesions	Slight arteriosclerosis; few arteriosclerotic scars; glomeruli large, hyperemic, cellular, partly infiltrated with leukocytes; swelling of capsular epithelium; much blood in tubules; many blood-casts; necrosis of epithelium; near glomeruli small areas of cellular infiltration and beginning formation of connective tissue.
edematous, opaque. es.	Few small arteriosclerotic scars; glomeruli large, very cellular; capsular spaces dilated, filled with granular material; leukocytes and red blood-corpuscles, beginning formation of fibrin; hemorrhages in many tubules.
; hemor-	Few small arteriosclerotic scars; glomeruli cellular; fusiform cells between loops and in capsular spaces, formation of fibrous tissue in some; many small foci of cellular infiltration; fatty degeneration of epithelium; hemorrhages and pigmented casts.

made to separate out the lead kidneys from the ordinary arteriosclerotic kidneys, but, I believe, with little success. In my specimens at least, I fail to find anything which would suggest any well marked difference.

The important rôle played by lead-poisoning in the production of these conditions is very clearly brought out by our tables, and it is particularly suggestive that among the severest cases in Table 5 the cases of lead-poisoning are especially numerous and well marked.

Below are given some data in regard to the interrelation of gout, on the one hand, and general arteriosclerosis and "arteriosclerotic nephritis," on the other. The frequent association of the two conditions is well known and hardly needs any additional confirmation. I may say that I have been interested in this relation for many years, even before these cases were collected. I am fairly positive, therefore, that gouty lesions were not overlooked in many instances, because they were carefully searched for.

Summary of Relation of Lead Poisoning and of Gout to Arteriosclerosis and Arteriosclerotic Nephritis

Among the 1,000 cases examined, lesions suggestive of gout were discovered in thirty instances. In twenty-three of these cases uric acid deposits were found in the kidneys only, in seven cases both in kidneys and in joints.

In eight of these thirty cases, the kidneys showed slight arteriosclerotic lesions only, curiously in all of these cases the deposits were limited to the kidneys. In three of the eight cases with slight renal lesions the hearts and blood-vessels were fairly normal; in the remaining five there was a marked general arteriosclerosis and cardiac hypertrophy. There were ten cases with large arteriosclerotic scars in the kidneys; in seven of these the deposits were confined to the kidneys; in three they were present in both joints and kidneys. In six of these ten cases the hearts and blood-vessels were fairly normal, whereas in four the arteriosclerosis was general and associated with cardiac hypertrophy. In twelve of the thirty gouty cases there was arteriosclerotic nephritis, which is nearly 50 per cent. of all cases of arteriosclerotic nephritis which were observed in the entire series of 1,000 cases. In these twelve cases, the deposits were found in the kidneys only eight times, in joints and kidneys four times. In all these cases the arteriosclerotic process was general and well marked with cardiac hypertrophy in all except one.

Among these thirty cases of gout, three were undoubted cases of lead-poisoning and in twelve others this was highly probable. Altogether then there were fifteen or just 50 per cent. of them which were probably due to lead.

There were three cases in which the occupation suggested chronic lead-poisoning, in which there was general arteriosclerosis, some renal lesions and cardiac hypertrophy without gouty manifestations.

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The findings in my cases seem to suggest that in gout quite generally the first deposits occur in the kidneys; also that the renal lesions associated with gout are practically always of the arteriosclerotic type. There is one apparent exception in our series; in Case 10 of the cases of acute and subacute glomerulonephritis (Table 6) gouty deposits were found in the pyramids. In this case, however, there is also present in the kidneys considerable arteriosclerosis with many arteriosclerotic scars. To a certain extent our observations support Müller's[24] statement that in lead-gout the lesions are apt to be much more serious than in gout due to other causes.

Fifty per cent. of our cases of gout were probably lead-gout — which, taking into account the rather imperfect histories which accompanied them, is a remarkably high percentage. Our cases also show clearly that chronic lead-poisoning in man eventually is practically always accompanied by gouty diathesis; only three exceptions were noted to this rule.

It is interesting to note that in 50 per cent. of all cases of "arteriosclerotic nephritis," gouty deposits were observed in the kidneys or in both joints and kidneys. Could gout be the result of the renal lesions, as has been suggested by some of the French authors? Hardly, when one takes into consideration those cases in which the renal lesions are so very slight.

As we know so very little about the true nature of the gouty diathesis, it seems premature to discuss its exact relation to the arterial and renal changes. I hardly think that it is safe to assume, from the evidence presented, that gout should be looked on as an etiological factor in the production of arteriosclerosis and arteriosclerotic renal lesions, although I myself was very much inclined to this view at one time. There are many other relations possible besides those of direct cause and effect between two phenomena which are frequently associated, the truth of which statement is not always sufficiently borne in mind in investigations of this character.

There remain to be considered forty-five cases of what Bradford[26] would consider true Bright's disease; of these, seventeen are cases of acute and subacute glomerulonephritis, all of a hemorrhagic character, seventeen others are large white kidneys all associated with amyloid, and eleven are secondary contracted kidneys in which we find a constant association of chronic glomerulonephritis with hemorrhages and a usually local deposit of a material which closely resembles, if it is not identical with, amyloid.

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ACUTE AND SUBACUTE GLOMERULONEPHRITIS

The seventeen cases representing this group are contained in Table 6. Several of them were encountered in comparatively young individuals. Practically all of them were suffering from a chronic septic process, most frequently from subacute or chronic septic endocarditis due to diplostreptococci. The condition is very similar in Case 2, in which we have a streptococcus sepsis following chronic pulmonary tuberculosis, in Case 4 with a pneumococcus sepsis following fracture, in Case 15 with a chronic sepsis following leg ulcer. In Case 10 there were large ulcers in the intestines which were possibly the portal of entry of a septic infection, because, so far as I know, mercurial poisoning in itself does not produce glomerulonephritis. In Case 12 the infection started from an abscess on one of the toes, in Case 13 there was scabies and general furunculosis, in Case 14 the septic process seems to have commenced in the lungs. In Cases 16 and 17, only the existence of a septic process is not definitely established but the numerous polymorphonuclear leukocytes in the renal lesions, at least in Case 16, make the existence of a septic process fairly probable.

The intimate relation of glomerulonephritis to chronic sepsis is also shown by the following figures: Among the 1,000 cases investigated, there were seventy-three cases of endocarditis; of these, ten were cases of recent and twenty-seven cases of healed endocarditis. No glomerulonephritis was found in these thirty-seven cases. Among the remaining thirty-six cases of subacute and chronic septic endocarditis, there were fourteen cases of glomerulonephritis.

Among the 1,000 cases there were also twenty-eight cases of general sepsis without endocarditis. Of these, twenty-one were acute and without glomerulonephritis, seven chronic, with glomerulonephritis in six.

The relation of sepsis to subacute and chronic nephritis has received some mention in literature, but its true extent has hardly been sufficiently appreciated. As early as 1884, Ernst[46] reports two cases of acute nephritis and one case of chronic parenchymatous nephritis with bacterial findings. In 1877, Bartels[11] mentions as etiological factors persistent suppuration, inveterate syphilis, phthisis and possibly malaria. Blum,[47] in 1890, states that chronic nephritis is caused by infectious diseases

46. Ernst: Zur Aetiologie der Nephritis, Zürich, 1884.

47. Blum: Ueber die Aetiologie der Nephritis, Deutsch. Arch. f. klin. Med., 1890, xlvii, 193.

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perhaps more frequently than is commonly believed, and reports a case, confirmed by autopsy, which followed parotitis epidemica. Councilman,[17] in 1897, found fifteen cases of sepsis in fifty-two cases of acute and subacute glomerulonephritis. Nicholls,[48] in 1899, believes that infection is important in all cases of chronic nephritis, having demonstrated to his satisfaction the presence of minute diplococci and sometimes of bacilli in the tissues and in the urine in many cases. Thompson[49] also points out the frequency with which chronic nephritis follows sepsis. In 1910, Curschmann[50] makes the very definite statement that sepsis is frequently the cause of acute and subacute nephritis of hemorrhagic type which, according to him, unfortunately frequently becomes chronic. He believes that it is usually toxic in origin but sometimes due to actual infection of the kidneys, when streptococci may appear in the urine. He also speaks of the relation of tonsillitis to these septic processes followed by nephritis, a matter which has also been discussed by other observers.

The most characteristic feature in the gross appearance of these kidneys with acute and subacute glomerulonephritis is the very marked diffuse hyperemia of the cortex, which is frequently associated with the occurrence of numerous plainly visible petechial hemorrhages. Often there is also considerable edema with swelling and the tissues are soft, putty-like. When there is much formation of pigment, the color of the kidneys may be distinctly brown, which was especially well marked in our Case 12. The surface of these kidneys is usually smooth but this may be somewhat modified by the pressure of arteriosclerosis and the development of arteriosclerotic scars.

Histologically, the glomerular lesions naturally attract most attention. There is hardly any other condition in the kidneys, or elsewhere for that matter, which has received as much careful study as the histology of glomerulonephritis, ever since it was first discovered by Klebs and described in his "Handbook of Pathological Anatomy." Goermans[51]

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48. Nicholls: Contributions to the Study of Bright's Disease, Montreal Med. Jour., 1899, xxviii, 161.

49. Thompson: Unsuspected Nephritis in Septic Infections, Brit. Med. Jour., 1907, ii, 737.

50. Curschmann: Beziehungen entzündlicher Mandelaffektionen zu Infektionskr., München. med. Wchnschr., 1910, lvii, 284.

51. Goermans: La Capsule de Bowman dans les infl. chroniques des reins, Rec. des travaux, anat. path. du lab. Boerhave, 1869.

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(1869), Langhans (1879,[52] 1883,[53] 1888[54]), Cornil and Brault (1885),[21] Obrzut[55] (1888), Ribbert[56] (1888), Boehm[57] (1897), Councilman[16] (1897), Cornil[58] (1900), Engel[59] (1901), Tschistowitsch[27] (1903), Herringham and Thursfield[60] (1904), and last but not least Löhlein[18] (1907), have published important contributions to this subject, and still there remains considerable uncertainty in regard to some of the finer histological detail. My impression is that, in many cases at least, there is first a hemorrhagic exudate poured into the capsular space of the glomeruli as shown in Figure 8, which coagulates and is later organized (see Figures 5, 6 and 7), a view strongly advocated by Cornil and by Engel. Eventually the process terminates in a more or less complete fibrosis of the affected glomeruli which is similar to that which occurs in arteriosclerosis but, to my mind, still sufficiently distinct to be differentiated from it, which differentiation is facilitated by the usual finding of the earlier unmistakable stages of the process even in very chronic cases of glomerulonephritis. Associated with this there are some interesting capsular changes which we need not dwell on here. I do not quite understand why Löhlein[61] in his last article on the subject wishes to separate those forms which occur in septic endocarditis from what he terms true glomerulonephritis. If he had fully recognized the importance of sepsis in the production of the lesions in all cases, I do not believe that he would have favored such an opinion.

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52. Langhans: Ueber die Veränderungen der Glomeruli bei der Nephritis, Virchows Arch. f. path. Anat., 1879, lxxvi, 85.

53. Langhans: Ueber die entzündlichen Veränderungen der Glomeruli, etc., Virchows Arch. f. path. Anat., 1885, xcix, 193.

54. Langhans: Ueber die entzündlichen Veränderungen der Glomeruli, Virchows Arch. f. path. Anat., 1888, cxii, 1.

55. Obrzut: Nouvelles recherches sur la pathogénie de la glomérulonephrite, Rev. de méd., 1888, viii, 689.

56. Ribbert: Beitrag zur path. Anatomie der Glomeruli, Fortschr. d. Med., 1888, vi, 490.

57. Boehm: Beitrag zur path. Anatomie der Malp. Körperchen der Niere, Virchows Arch. f. path. Anat., 1897, cl, 52.

58. Cornil: La glomérulité, Presse méd., 1900, xviii, 1, 177.

59. Engel: Glomerulitis adhæsiva, Virchows Arch. f. path. Anat., 1901, clxiii, 209.

60. Herringham and Thursfield: The Glomerular Lesions of Diffuse Nephritis, Tr. Path. Soc., London, 1904, lv, 283.

61. Löhlein: Pathol. Anatomie der hæmatogenen Nephritis, Ergebn. d. allg. Path. u. path. Anat. (Lubarsch and Ostertag), 1910, xiv, ii, 874.

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The presence of many polymorphonuclear leukocytes in the blood-vessels and in the hemorrhagic exudate is very characteristic and well shown in Figure 6. Blood-casts and pigmented hyaline casts are naturally frequent. The epithelium usually shows well-marked degenerative changes, often ending in necrosis. In practically all cases there is some cellular infiltration, at least in the vicinity of the diseased glomeruli, and eventually there may be quite a considerable, more or less diffuse proliferation of the interstitial tissue with formation of fibrous tissue and shrinkage. The inflammatory changes in the glomeruli and those in the interstitial tissue seem to be widely independent from one another. This is most clearly illustrated by Case 17 (VIII-76), in which there is remarkably little change in the glomeruli and a very well-marked diffuse overgrowth of the connective tissue.

There is also no constant relation between the extent of the disease in the glomeruli and the amount of epithelial degeneration which one should expect, according to Löhlein's theory that the epithelial changes depend on circulatory difficulties resulting from the disease of the glomeruli. I feel constrained to assume that the epithelial lesions are toxic in origin and I cannot feel that there is as little foundation for such an assumption as Löhlein wishes us to understand.

It does not coincide very well with Loeb's[62] idea, that there is a particularly close relation between glomerular disease and hypertension followed by cardiac hypertrophy, when we notice that in those cases in which other reasons for cardiac hypertrophy are absent, the hearts are uniformly small. In Cases 12, 13, 14 and 15 only is there a slight hypertrophy which, however, as there is evidently no other factor to explain it, must be definitely ascribed to the condition of the kidneys.

LARGE WHITE KIDNEYS WITH AMYLOID DEGENERATION

After what has been laid down in literature on the subject, it is certainly quite surprising to find that not only all large white kidneys in our series are associated with amyloid but also that in all cases of amyloid degeneration, in which the condition was well advanced, there was a large white kidney associated with it.

Among the 1,000 necropsies there were thirty-seven cases of amyloid degeneration; nine of these showed incipient lesions, either in the spleen

62. Loeb: Blutdruck und Herzhypertrophie bei Nephritikern, Deutsch. Arch. f. klin. Med., 1905, lxxxv, 348.

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only (six cases), in spleen and liver only (one case) or just beginning amyloid of the kidneys (two cases). The rest showed associated parenchymatous nephritis. In three of these, the lesions were in the incipient stage, in the others there are well-developed large white kidneys. The close relation between amyloid degeneration and large white kidneys has, of course, been known to all observers, but a differentiation between amyloid kidneys and chronic parenchymatous nephritis has been attempted again and again, most frequently "for clinical reasons."

Apart from this, my series adds only little to what is already well known. The gross appearance of these kidneys has been described too often to need further comment.

The incipient glomerular lesions are well shown in Figure 8, which also brings out one important point, namely, that from the beginning there is considerable, often quite diffuse cellular infiltration of the interstitial tissue which seems to commence in the vicinity of the glomeruli. In the beginning there is sometimes a very marked infiltration of the tissues with polymorphonuclear leukocytes. The presence of leukocytes and, especially in the later stages, of blood in the tubules connects these cases with my series of acute and subacute glomerulonephritis, which connection appears particularly close when we notice that almost from the beginning the amyloid degeneration of the glomeruli is associated with signs of glomerulonephritis, which after a while become more evident and eventually leads to fibrosis as shown in Figure 9. At this time, the chronic interstitial changes are well marked and evidences of shrinkage make their appearance. The epithelial lesions are well marked in all cases and show practically in all instances the peculiar coarsely granular degeneration in which doubly refracting lipoidal granules or droplets make their appearance in the protoplasm, a condition which has quite a literature of its own.

The presence of an immense number of casts is also quite characteristic of this type of renal lesion.

Etiologically also the two groups have much in common. The relation of chronic sepsis to amyloid degeneration is too well understood to need any mention. In chronic pulmonary tuberculosis, which is the most common cause of these large white kidneys, we have a typically septic condition with well marked general intoxication. Syphilis can be easily looked on as a peculiar type of general sepsis. This disease may also cause some predisposition to cryptogenic septic infections. It is interest-

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ing to note the comparatively large number of cases of cirrhosis associated with large white kidneys (Cases 9, 10, 13, also Case 19 of the next group), which to my mind throws an interesting sidelight on this disease which still appears so very obscure from many points of view.

The blood-vessels are normal or show accidental lesions; it is also a well-known fact that in these cases the heart is usually small, sometimes normal and very rarely enlarged. In my series, the latter is the case in one instance only (Case 9). It is possible that there was sufficient general arteriosclerosis present in this instance to account for this apparent exception.

SECONDARY CONTRACTED KIDNEYS

It is to a great extent due to Löhlein's[19] work that the comparative frequency of secondary contracted kidneys has been definitely proved. The older authorities, in Germany at least (like Bartels), look on them as great rarities. Occasional cases were reported by Dickinson,[9] Leyden,[23] Aufrecht,[63, 59] Held,[64] and Eisenlohr.[65] Cornil[21] surmised that many cases of old contracted kidney might have had a more acute inflammatory origin, but did not prove his point by any direct observation. From the clinical and pathological material in Leipsic, Löhlein[19] succeeded in collecting quite a number of cases which clinically as well as anatomically were evidently examples of secondary contracted kidneys. He found in all of them changes in the glomeruli referable to former glomerulonephritis and points out that, on account of the comparative ease with which he discovered such cases, they cannot be so rare as was formerly believed.

My observations bear this out in every respect, except that in addition to the ordinary glomerulonephritis there is present usually in the glomeruli a peculiar hyaline substance which, in some cases I am sure, is amyloid. In others it was not discovered until after the specimens had been hardened and the possibility of obtaining a typical reaction was more or less interfered with by the hardening process. When tested with methyl violet, the reaction in these cases was at least as strong as in other specimens with known amyloid. It will remain for the future to decide

63. Aufrecht: Eine 20 Jahre dauernde Nephritis, etc., Deutsch. Arch. f. klin. Med., 1888, xlii, 517.

64. Held: Zur Kenntnis der glatten weissen Schrumpfniere, Beitr. z. path. Anat., 1889, vi, 133.

65. Eisenlohr: Zur Entwicklung der Schrumpfniere aus acuter Nephritis, Deutsch. Med. Wchnschr., 1892, xviii, 723.

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TABLE 7.—Continued. CHRONIC PARENCHYMATOUS NEPHRITIS

Number and Age	Probable Cause	Extent of Amyloid	Heart	Blood-Vessels
21 VIII-22	Sepsis suspected but not proved.	Kidneys only.	Slight hypertrophy and dilatation of left ventricle.	Slight general arteriosclerosis.
22 VII-85 Old man.	Chronic leg ulcer.	Spleen, adrenals, kidneys.	Brown atrophy.	Normal.
23 V-50 Middle age; painter.	Sepsis suspected but not proved.	Kidneys and possibly spleen.	1¼ times normal.	Very marked general arteriosclerosis.
24 VII-39 39 yrs.	Sepsis suspected but not proved.	Kidneys only.	1½ times normal.	Slight atheroma of aorta.
25 XII-57 43 yrs.	Sepsis suspected but not proved.	Kidneys only.	1¼ times normal; marked concentric hypertrophy of left ventricle.	Slight arteriosclerosis.
26 VI-14 45 yrs.	History of scarlet fever; sepsis suspected but not proved.	Kidneys only.	2 times normal.	Slight atheroma of aorta; moderate peritoneal arteriosclerosis.
27 VI-60 54 yrs.	Sepsis suspected but not proved.	Kidneys only.	3 times normal.	Slight atheroma of aorta.
28 XIII-110 38 yrs.	History of articular rheumatism; sepsis suspected but not proved.	Kidneys only.	Very large marked hypertrophy of left ventricle.	Slight atheroma of aorta.

TABLE 8.—ASCENDING S

Number and Age	Other Lesions	Heart	Blood-Vessels	K
1 XIII-105 70 yrs.	Carcinoma of rectum extending into bladder; nodular hypertrophy of prostate.	Brown atrophy.	Slight atheroma of aorta.	Large, soft, cortex red definite.
2 V-44 64 yrs.	Death from cerebral embolism; purulent cystitis.	Fatty heart.	Normal.	Left, 11×4 flat scars
3 XIII-78 60 yrs.	Nodular hypertrophy of prostate; gangrenous cystitis; small papilloma of bladder.	Normal.	Moderate atheroma of aorta.	⅔ normal si cortex red
4	Diverticula of bladder; gravel	Hypertrophy re-	Marked atheroma	Left, 9×4× large ret

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S AND AMYLOID DEGENERATION. II. SECONDARY CONTRACTED KIDNEYS

Kidneys: Gross Appearance	Kidneys: Microscopic Lesions.
11½ × 5½ × 2½ cm.; surface somewhat granular; cortex opaque, full of yellow spots.	Marked arteriosclerosis; much amyloid in glomeruli; marked sub acute and chronic glomerulonephritis; much granular and fatt degeneration of epithelium; many casts; much blood and leuk cytes in tubules; much new-formed connect. tissue with shrinkag
8½ × 3 × 4½ cm.; capsule thick; surface coarsely granular, mottled; cortex much reduced.	Very marked arteriosclerosis; much amyloid in glomeruli; marke subacute and chronic glomerulonephritis; much fatty degener tion of epithelium; very many casts; many leukocytes in tubules much new-formed connective tissue with shrinkage.
10½ × 5½ × 3½ cm.; slightly granular, mottled; cortex about 4 mm. wide.	Marked arteriosclerosis; some hyaline glomeruli; moderate amoun of amyloid in glomeruli; subacute and chronic glomerulonephritis much granular and fatty degeneration of epithelium; very man casts; blood and leukocytes in tubules; thrombosis and leukocytos in blood-vessels; much new-formed connect. tissue with shrinkage
Left, 12½ × 3½ cm.; right, 9 × 5 × 2¼ cm.; granular, mottled; many small cysts in left kidney.	Marked arteriosclerosis; moderate amount of amyloid in glomeruli subacute and chronic glomerulonephritis; much granular and fatt degeneration of epithelium; many casts; leukocytes in tubules very much new-formed connective tissue with shrinkage.
Moderate size; capsule adherent; surface granular; many hemorrhages; many yellow spots in cortex, which is reduced in size; large uric acid calculi in both renal pelves.	Marked arteriosclerosis; much amyloid in glomeruli; marked sub acute and chronic glomerulonephritis; marked granular fatt degeneration and necrosis of epithelium; many casts; much blood and some leukocytes in tubules; much new-formed connective tissue with shrinkage.
13 × 5 × 3 cm.; surface granular; cortex reduced, shows some hyperemic spots.	Moderate arteriosclerosis; moderate amount of amyloid in glomeruli; marked subacute and chronic glomerulonephritis; some granular and much fatty degeneration of epithelium; very many casts; leukocytes in tubules; much new-formed connective tissue with shrinkage.
9½ × 4½ × 3 cm.; surface granular; cortex much reduced.	Extreme arteriosclerosis; moderate amount of amyloid in glomeruli; marked subacute and chronic glomerulonephritis; many casts; much blood and some leukocytes in tubules; much new-formed connective tissue with fatty degeneration and shrinkage.
⅔ normal; surface granular, pale, with reddish patches; cortex thin, hard, many calcareous (?) infarctions in pyramids.	Moderate arteriosclerosis; much amyloid in shrunken glomeruli; marked chronic glomerulonephritis; fatty degeneration in atrophied and in few remaining large tubules; many casts; blood and leukocytes in tubules; very much new-formed connective tissue with much shrinkage.

SUBACUTE AND CHRONIC NEPHRITIS

Idneys: Gross Appearance	Kidneys: Microscopic Lesions
surface finely granular, mottled; uced in places, opaque; marking in-	Large arteriosclerotic scars; in some sections large areas of cellular infiltration and new formation of cellular connective tissue; much fatty degeneration tubules and in connective tissue; leukocytes in tubules.
× 3½; right, 10 × 5 × 3 cm.; large on surface.	Some arteriosclerotic scars; marked diffuse thickening of interstitial tissue.
ze: surface rough, with purple scars;	Marked arteriosclerosis, few arteriosclerotic scars; marked diffuse somewhat irregular fibrous thickening of interstitial tissue with some cellular infiltration; atrophy of tubules in worst places.
face granular, with many ars. some hydronephrosis;	Little arteriosclerosis; few hyaline glomeruli; large areas of cellular infiltration and new formation of fibrous tissue with

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whether the substance is real amyloid in all cases. It is certainly closely related to it. It stains for instance exactly like amyloid with the van Gieson method. The occurrence of this peculiar "hyaline" in chronic glomerulonephritis has been described before by Councilman[17] and others. On account of the presence of this substance, I have appended the list of these cases to the list of large white kidneys with amyloid degeneration, and neither macroscopically nor microscopically is there a sharp line of division between them. With the same degree of propriety, however, this series could be looked on as a continuation of the series of cases of acute and subacute glomerulonephritis. The amount of amyloid-like substance and the degree of typical glomerulonephritis exhibited varies considerably in the different cases. A more detailed description may be found in the second part of Table 7.

In all cases there are blood and leukocytes in the tubules, the epithelial degenerations are well marked and casts are more or less abundant.

It is only natural that in these very chronic cases the relation to the original sepsis is not so clear as in the more acute cases of glomerulonephritis and of large white kidneys. In one case there existed a chronic leg ulcer (Case 22), in another there is a history of scarlet fever (Case 26), and in a third a history of attacks of articular rheumatism. In the others, I have surmised the existence of an obscure sepsis on account of the evidences of sepsis in the kidneys and also on account of the intimate relation of chronic sepsis with the more acute cases out of which these secondary contracted kidneys evidently develop. It will be interesting to see whether in the future the relation of these cases to certain septic processes can be established by direct evidence.

The overgrowth of the interstitial tissue is very well marked, much more so than in the ordinary arteriosclerotic kidneys and the evidences of shrinkage are unmistakable. I give several illustrations of this type of renal lesion as it is not as well known as the others.

Fig. 10 (Case 20, VIII-47) shows a condition very similar to that which occurs in old amyloid kidneys, only to an exaggerated degree.

Fig. 11 (Case 21, VIII-22) belongs more properly to the chronic glomerulonephritis, still there is much of the amyloid-like material in the glomeruli.

Fig. 12 (Case 24, VII-39) is taken from a kidney with very marked fibrous proliferation of the interstitial tissue and very marked shrinkage. The glomerulonephritis is well marked.

There is nothing in the gross appearance of these kidneys which would permit one to make a diagnosis of the condition with certainty.

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They are neither all typical white contracted kidneys, nor is the peculiar coarsely lobulated appearance, described by others, at all pathognomonic for this condition. The presence of visible hemorrhages as in Case 25, XII-57, might be suggestive, as they are not so apt to occur in arteriosclerotic contracted kidneys, but it is only on careful microscopic examination that a definite decision can be reached. Then the presence of the amyloid-like material in the glomeruli, the evidences of subacute and chronic glomerulonephritis, the pronounced and somewhat peculiar degenerative changes in the epithelium, the many casts, and the presence of blood and leukocytes in the tubules will help to settle the differential diagnosis.

The relation of this condition, which is evidently primarily renal, to heart and blood-vessels is naturally of particular interest. It is quite frequently associated with arteriosclerosis both in the kidneys and elsewhere. If we look over the records, we find marked and sometimes extreme arteriosclerosis in the kidneys in all, except in one case (Case 20, VIII-47). General arteriosclerosis is much less common. In two cases the aorta and the peripheral blood-vessels are normal, there are slight lesions in six cases, leaving three only in which there is well-marked atheroma of the aorta or peripheral arteriosclerosis or both. In one case, in a syphilitic, there is an aneurysm of the arch.

It almost looks as if the arteriosclerosis in the kidneys was secondary to the chronic inflammation in the tissues, as has been suggested repeatedly. This interpretation, however, could not be accepted if with Jores we distinguish sharply between true arteriosclerosis and the endarteritis obliterans which accompanies chronic inflammatory processes, because in these cases there is marked splitting up of the internal elastic membrane in the intimal thickening which, according to Jores,[63] would rule out local inflammation as a cause of it. I am not quite convinced, however, that this distinction drawn by Jores is entirely justified.

We might also explain the comparative rarity of general arteriosclerosis by assuming that it develops late following the full development of the condition in the kidneys.

These are surmises, purely, and I believe that the latter has somewhat less ground to stand on than the former.

The condition of the heart also varies very much. In one case there is brown atrophy, in five cases the heart is only moderately enlarged and

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in the last three cases only, which, however, represent the extremes of the process, the hypertrophy of the heart is at all considerable.

I submit that if it is difficult in arteriosclerotic kidneys to unravel the threads which bind these peculiarly associated conditions together, it is still more difficult to do so in the case of secondary contracted kidneys. We can again gather an obscure suggestion that there may be some relation between destruction of kidney-tissue and the development of cardiac hypertrophy, directly or indirectly, but what the relation is seems still very much unsettled. The renal lesions, however, evidently must be very extensive to become effective, which corresponds somewhat with the results of experimental research and is also confirmed by observation in those cases in which the kidneys are destroyed by ascending non-suppurative nephritis, for instance, in cases of chronic cystitis and pyelitis following prostatic hypertrophy, of renal calculi and of malignant tumors in prostate and cervix uteri. It has been repeatedly pointed out, and it is also borne out by my personal observations, that in such cases we may have much destruction of renal tissue and very marked shrinkage of the kidneys, without any cardiac hypertrophy. I have collected reports of eight such cases among my records (see Table 8), and only in one is there the slightest evidence of any hypertrophy. In this case, the heart was stated to be one and one-fourth times normal in size, truly, not a very striking change.

It is from the experiment that we must hope for the solution of all these grave problems, but the experiment alone will not guide us, unless it is supplemented by sound knowledge of the conditions as they actually exist in man.

CONCLUSIONS

The following would be a short summary of my conclusions.

At the present time, in many cases entirely too much attention is paid to the kidneys, clinically and anatomically.

The so-called primary or genuine contracted kidney represents a disease of the kidney which is the result of arteriosclerosis in the terminal arterioles in this organ, is closely associated with general arteriosclerosis and cannot be properly understood without due consideration of this fact.

It is difficult to decide the exact interrelation between the renal lesions, general arteriosclerosis, and the hypertension and cardiac hypertrophy which is usually present in these cases. It is only safe to say that

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the rôle of the kidney lesions in the production of the hypertension has been evidently considerably exaggerated.

There is some reason to believe that the condition as a whole is a toxic one. So far, however, lead is the only substance which seems to bear any definite etiological relation to the general process.

Of true primary subacute and chronic inflammations of the kidneys there remain subacute and chronic glomerulonephritis, definitely in the majority of instances due to chronic sepsis.

Closely related to this, etiologically and anatomically, is the subacute and chronic amyloid kidney (the large white kidney of other authors).

From a combination of these last two conditions there arises the so-called secondary contracted kidney which in our series was responsible for eleven out of thirty-seven cases of seriously contracted kidneys,

The etiology of the cases of secondary contracted kidney is not quite so clear as that of the more acute conditions but it is highly probable that chronic sepsis, in the broadest sense, is an important factor.

The lesions in subacute and glomerulonephritis and secondary contracted kidneys are practically always hemorrhagic, and in subacute and chronic amyloid kidneys frequently so.

The interstitial lesions which are present in these latter conditions begin to develop early, practically simultaneously with the epithelial lesions. It is not very likely, therefore, that they should be secondary to them.

ABSTRACT OF DISCUSSION

Dr. Leo Loeb, St. Louis: I would like to ask if the author has paid any attention to the adrenals in nephritis.

Dr. W. Ophüls, San Francisco: I have paid some attention to them, not very much, however, because from my studies of the literature I was not encouraged to undertake a careful investigation of the adrenals. Most authors who have gone into the condition carefully have come to the conclusion that the adrenals do not play an important part in the tension of arteriorenal disease.

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